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ORIGINAL CONTRIBUTIONS

THE TECHNIC OF NUTRITIONAL THERAPY—*Morton S. Biskind, M. D.* 57

TRANSPYLORIC PROLAPSE OF GASTRIC MUCOSA—*W. P. Kleitsch, M. D. and R. L. Lawton, M. D.* 67

AN UNDERSTANDING OF PROLAPSED GASTRIC MUCOSA—*Francis W. Wilson, Lt. Col., USAF* 71

MEMBRANOUS STAPHYLOCOCCAL ENTERITIS AFTER ANTIBIOTIC THERAPY: REPORT OF TWO CASES—*William J. Brown, M. D., Rose Winston, M. D. and Sheldon C. Sommers, M. D.* 73

PRELIMINARY REPORT ON THE EFFECT OF SMOKING ON THE ASCORBIC ACID CONTENT OF WHOLE BLOOD—*Anne Bourquin, Ph. D. and Elena Musmanno, M. S.* 75

PRACTICAL DIAGNOSIS OF PANCREATIC DISEASE—*H. M. Spiro, First Lieutenant, MC* 78

EDITORIAL, BOOK REVIEWS, GENERAL ABSTRACTS OF CURRENT LITERATURE 85-90

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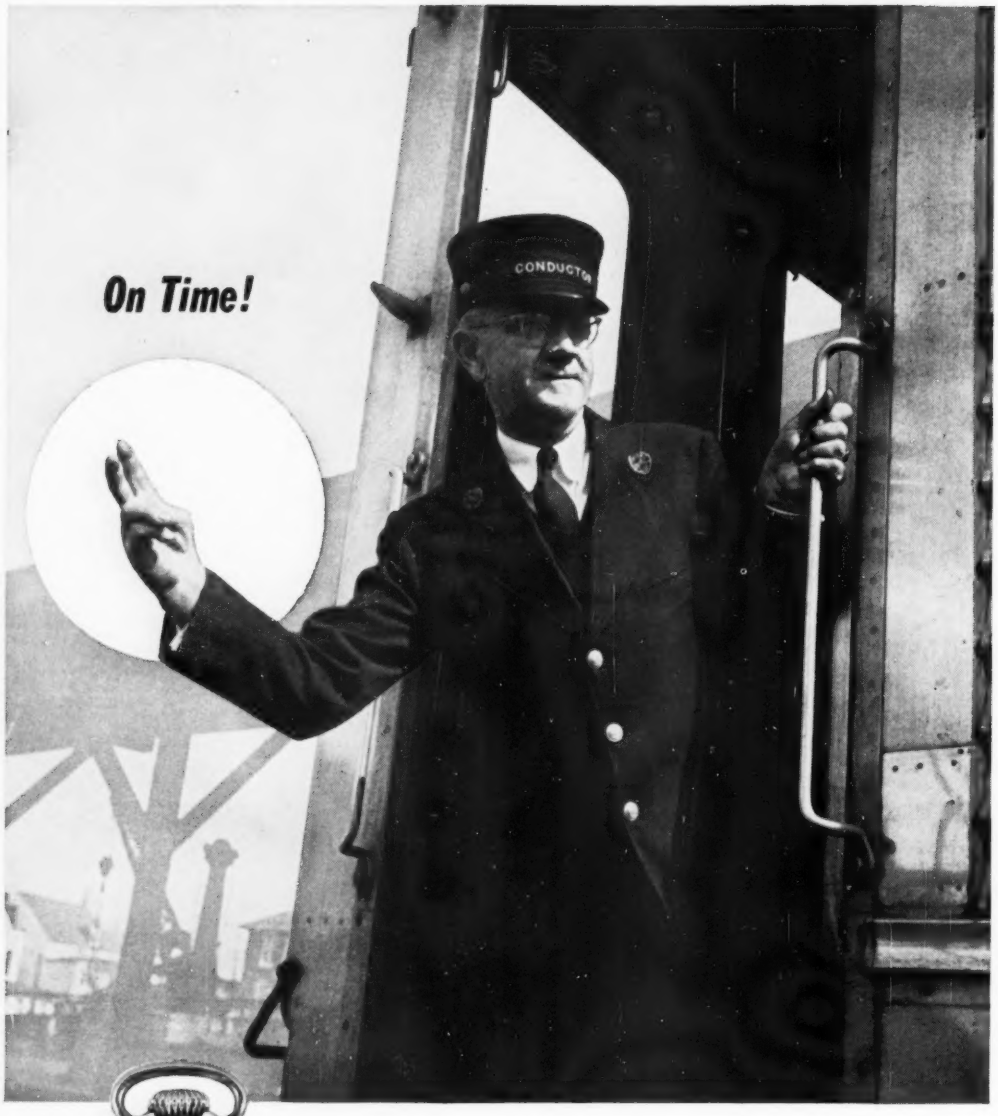

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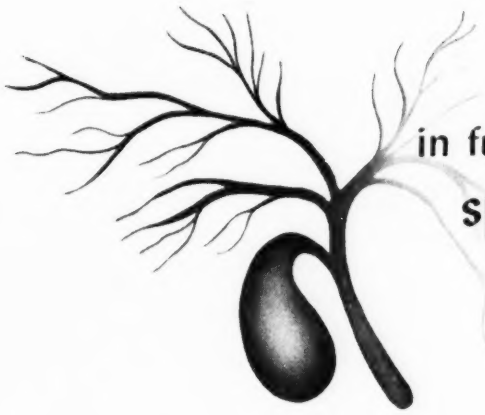

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For reasons not entirely understood at present, "heart disease and high blood pressure are more common in overweight persons than in those of desirable weight." The predisposition to atherosclerosis in obesity and the increased physical burden of carrying excess weight are undoubtedly contributing factors. Hence, as this publication points out, weight reduction is the first line of defense in decreasing the incidence of cardiac disease, and in improving the prognosis after cardiac disease or hypertension has developed.

Meat occupies a prominent position in the weight reduction diets outlined in this American Heart Association booklet. This recommendation is in sharp contrast to the erroneous belief held in former years that meat is harmful in hypertension or cardiac disease. "There is no evidence that red meat or any other form of protein in moderation has any adverse influence on blood pressure."

The magic formula for reducing is simply "Eat less." Two types of diets are outlined. One "allows moderate amounts of meat and other proteins, small amounts of fat and moderate amounts of carbohydrates." The other is "high in protein with plenty of meat, eggs and cheese, moderate in fat and low in carbohydrates." Diet No. 1 provides 70 Gm. of protein, 60 Gm. of fat, and 120 Gm. of carbohydrate; caloric yield, 1,300. Diet No. 2 provides 100 Gm. of protein, 80 Gm. of fat, and 60 Gm. of carbohydrate; caloric yield, 1,360.

The inclusion of generous amounts of meat in these diets—12 to 16 ounces of cooked meat or two substantial servings each day in Diet No. 2—is a reflection of the important role meat plays in any weight reduction regimen. It is generously included because of its high content of protein of excellent biologic value and because lean meat contains unobjectionably small amounts of fat.

*Food For Your Heart, a Manual for Patient and Physician, Department of Nutrition, Harvard School of Public Health, Harvard University, The American Heart Association, Inc., New York, 1952. Copies available through local Heart Association.

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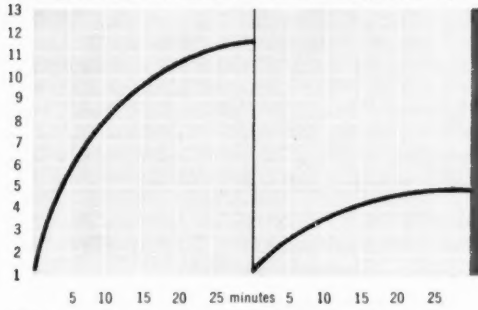

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2. *Smith, F. H.:* Gastroenterology, *8:494, Apr., 1947.*

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THE TECHNIC OF NUTRITIONAL THERAPY

MORTON S. BISKIND, M. D., Westport, Connecticut.

Accumulating evidence emphasizes more and more the complexity of the nutritional needs of the animal organism. From a few nutrients thought to be adequate for healthy cellular metabolism a generation ago, the number of factors known to be necessary has grown enormously. The dramatic recent progress made in the chemical identification and synthesis of essential dietary principles has had a salutary effect in providing therapeutically potent quantities of the newly discovered substances. However, this has also had another and less salutary effect.

Tradition in modern medicine has for some years been toward the use of single drugs. In reaction to the unscientific multiplicity of inert or therapeutically ineffective ingredients that characterized the usual prescription several decades ago, this was an important progressive step for pharmacology. But with the increasing availability of chemically pure dietary essentials, the tendency to administer single substances in relatively large amounts has carried over into the field of nutrition. At the least, administration of therapeutic doses of single substances (or even incomplete groups of them) is either only partially effective or even altogether ineffective. At the most it may actually be harmful.

In addition, several misconceptions that are derivatives of modern trends in therapeutics, have become increasingly prevalent. One common misconception is that all the important nutritional elements have already been isolated, and indeed, that a number of those currently available are not significant in human nutrition. The extremely conservative attitude of the Federal Food and Drug Administration which requires disclaimers on labels of vitamin preparations for the vitamins they consider not adequately studied in human nutrition, has further fostered the assumption that administration only of the pure factors thus far considered "important" is sufficient for satisfactory nutritional therapy.

Another misconception is that deficiencies of single factors occur in human beings. This has been perpetuated mainly by some erroneous propositions commonly expressed in the literature on nutritional research. "Thiamine deficiency," "niacin deficiency," "riboflavin deficiency," and the like are used in publications under the assumption that they refer to pure uncomplicated deficiencies of single factors. Yet at the present state of nutritional research the impossibility of attaining this desirable end with any single vitamin is manifest. Obviously, until all the essential elements have been isolated and made available in sufficient quantities for supplementation of a vitamin-free basic diet, it is not possible to omit just one element without complicating the deficiency by the lack of all the essential elements yet unknown or unavailable. Thus, to produce "thiamine deficiency" an animal would be placed on a vitamin-free diet to which has been added all the available pure vitamins except thiamine. The deficiency produced is a deficiency of thiamine plus that of all the other factors not yet isolated. Added to this is the fact that a deficiency of this type is rapidly complicated by loss of other essential substances from the body stores. And, when thiamine is administered to such an animal and an effect noted, this cannot be assessed as an uncomplicated function of thiamine. It merely indicates what thiamine can do (within the time limits of the experiment) in the absence of other essential factors. When all the essential nutrients have been isolated it will be necessary to re-assess the functions of each.

In the human being, how much more unlikely that deficiency of single factors should occur. Factors which lead to the loss of thiamine, for instance, inevitably lead to the loss of other substances that occur with it, have similar solubilities or are also labile to heat, alkalinity or oxidation. Similarly, "conditioning" factors which operate to produce deficiencies even on an optimum diet, tend inevitably to produce deficiencies of several factors at once. Not only are deficiencies multiple but the administration of single nutritional factors or even of a combination of a few of them may actually lead to serious disturbance of a tenuous nutritional equilibrium and precipitation of new avitaminotic lesions. Those familiar with the history of the early use of niacin in the treatment of pellagra will recall the glowing preliminary reports of healing of the skin lesions and the glossitis soon to be followed by pessimistic accounts of the appearance of secondary lesions, such as cheilosis and peripheral neuritis. The addition of an adequate natural source of nutritional factors to the therapeutic regime led to prompt subsidence of all the lesions. Similarly, in a recent study on the treatment of the peripheral neuritis of beri-beri in prisoners of war, administration of thiamine alone failed to affect the neuritis although there was definite amelioration of this lesion in patients who received the whole B complex.

For many years, investigators with experience in nutritional disorders have stressed the necessity for complete therapy. This of course requires the inclusion in the therapeutic regime of an adequate amount of a satisfactory source of the as yet unidentified essential factors. In the course of developing an adequate nutritional regime, Spies suggested some years ago, a "basic vitamin formula," consisting of thiamine, riboflavin, ascorbic acid and niacinamide. Inherent in the choice of the name "basic" was the intention that a preparation of this type be used only as the framework of the regime and that other substances, including an adequate natural source of nutritional factors, be added to it as the condition of the patient requires. But a further development soon supervened. Vitamins A and D were added to this preparation, to which of course there is no objection; but unfortunately, the new product was for a long time called "therapeutic vitamin formula." This name no longer carried the connotation of incompleteness and an amazing tendency rapidly developed into widespread practice for the use of such preparations as the sole source of nutritional elements. Many physicians administer such preparations under

Submitted Sept. 26, 1952.

the impression that they provide all the important vitamins. As a result numerous therapeutic failures occur and nutritional conditions which would have been responsive to adequate therapy are considered to be other than avitaminotic in origin or to be completely refractory. This has repeatedly been observed by the author, who has seen numerous patients thus treated with a therapeutic vitamin formula over long periods who derived little or no benefit or who actually became worse. Simply adding desiccated liver or suitable liver fractions to the regime invariably has resulted in a dramatic and lasting improvement, often evident within a few days.

Forms of the "therapeutic formula" type of preparation which contain in addition to the six factors mentioned, pyridoxine, folic acid, pantothenic acid and tocopherols, represent an improvement over the original but these still fall far short of completeness, with regard to available crystalline vitamins, and even more so with regard to the unidentified essentials.

A few citations from recent literature should suffice to illustrate the growing evidence that a number of unidentified substances occur in liver that are at least as important to nutrition as many of the factors already known. Among these are: a heat stable factor or factors present in whole liver (but not significantly in aqueous extracts) effective clinically in healing certain types of glossitis (10, 11); a substance or substances in the non-saponifiable lipoid fraction (103) which is essential to normal liver function (inactivation of estrogen) (10, 11); liposoluble substances essential to the production of granulocytes and lymphocytes (99); a substance or substances in the non-saponifiable lipoid fraction that prevents the rusting and dermatitis that otherwise result in estrogen-treated rats on a vitamin B complex-free diet (10); a factor soluble in methanol which is essential to nutrition in the mink and the fox, and still another factor necessary to these animals which resides in the remaining portion of the liver (28); a heat stable substance or substances which occurs in the non-water soluble portion of liver that prolongs the lives of rats receiving toxic doses of thyroid or of certain drugs such as atabrine or dinitrophenol (45-47); a substance occurring in desiccated whole liver but not in antianemic liver extracts that promotes the growth of rats fed thyroid (6); a substance appearing in the non-water soluble fraction of liver that is involved in the production of intestinal xanthine oxidase (83); a principle occurring in whole liver but not in aqueous extracts, necessary to the prevention of anemia in the monkey (28); a heat-stable substance in whole liver soluble neither in aqueous nor lipid solvents that has anticarcinogenic properties (74); a substance in whole liver which promotes resistance to fatigue (48); a heat stable factor called vitamin B_T essential to certain larvae, present in liver, yeast and milk (50), recently isolated from liver and identified as carnitine (27).

Of course, as only one of these factors has been identified, some may be identical; but the presence of essential factors in aqueous, lipoid and protein fractions of liver other than the known crystalline vitamins is now undisputed. It should be emphasized that, as indicated in several of the investigations cited, yeast (probably the most commonly used source of the natural B complex) provides either a poor source of one or more of these substances or contains none at all (for instance, yeast does not contain vitamin B_{12}). That this applies clinically, has also been amply demonstrated, and is well illustrated in a case cited by Cahn (25). This was a case of chronic hypertrophic gingivitis in which the administration of six teaspoonfuls of desiccated liver led to rapid regression of the gingival lesions. Substitution of granular yeast for the liver led to recrudescence of the gingivitis which disappeared again when powdered liver was given and remained healed so long as the latter was continued. As Cahn states, "This illustrates what all nutritionists have learned, that liver supplies some fraction that yeast does not." Similar observations have repeatedly been made by the author and his associates in treating a variety of nutritional defects and their resultant endocrine disturbances. Suitable liver preparations and especially desiccated liver were found to be incomparably superior to yeast and rice bran extract as a source of therapeutically effective nutrients. Yeast and rice bran are nevertheless very useful and do provide some of the necessary unidentified factors when given in sufficient dosage. For whole dried yeast this would represent from three to six ounces a day. (How nearly insignificant then are the few grains of brewers yeast per capsule or tablet included in numerous commercial vitamin preparations as a source of accessory factors!) Yeast extracts, however, considerably more concentrated, are effective in correspondingly smaller doses, two or three heaping teaspoonfuls a day. Yeast extract or rice bran extract, or both, may effectively be combined with liver preparations.

Returning again to therapeutic liver preparations, another widespread misconception confronts the therapeutist. Since the advent of antianemic liver preparations, the idea that such products represent *all* the effective agents in liver has gained increasing currency. So compelling is this attitude that some investigators who have used such preparations in nutritional disorders, dismiss liver together as a therapeutic agent, because these products are ineffective in conditions for which they were never intended. Parenteral liver extracts especially, even the so-called "crude" extracts (which, from the standpoint of the nutritional content of the original whole liver are not really "crude" at all but represent considerable fractionation), are purified with a view to increasing their antianemic potency. In this process almost all the B vitamins, except B_{12}, separate out into the portion of the aqueous extract that is discarded (not to mention the factors remaining in the lipoid and protein fractions). Thus only small traces of the B vitamins remain in these extracts as impurities; the amounts are so small as to be almost insignificant therapeutically unless doses so large are employed (20 to 40 cc. per day) as to approach or exceed the limits of therapeutic expediency. Obviously, most of the total commercial output of the antianemic liver preparations is used for conditions other than macrocytic anemia. In the days before B_{12} became the antianemic standard, there were not enough cases of Addisonian anemia even to assay samples of successive batches of the commercial products, and the remaining groups of patients that provide legitimate indications for antianemic liver extracts are far from populous enough to use up the tremendous annual output. Large amounts of whole liver are withdrawn from the

market and fractionated and vast quantities of essential nutrients are thus diverted from human use. The whole liver from which the extracts are made, if used as food, would provide dramatically superior results, for maintenance and treatment.[1] In a case described by the author, administration of 5 cc. per day of a 2 unit per cc. "crude" antianemic liver extract for thirty days failed to have a perceptible effect on a severe atrophic glossitis. Oral administration of cooked whole liver in quantities much smaller than those from which the ineffective extracts were derived, led to prompt and complete healing of the glossitis (10, 11). For years, one manufacturer had by far the best vitamin B complex preparation on the market because portions of the liver fractions remaining after preparation of the antianemic extracts were included as a source of the accessary factors, a practice which other firms adopted only after considerable delay. But of course, even these products, superior as they may be, unless they contain whole liver, lack some of the essential elements.

A final misconception requires discussion. This, most common perhaps of all, really involves three separate elements. These are: 1. That the average American diet supplies all the necessary nutritional elements in adequate amount; 2. That nutritional deficiency when it does occur results only from dietary deficiency; and 3. That all that is necessary to cure lesions of nutritional deficiency is a "good" diet.

As to the first of these, that the average American diet is adequate, evidence to the contrary is so overwhelming that it is surprising that this belief continues to be so widespread (3, 24, 39, 67, 72, 93, 94, 97). Among the factors involved in the depletion of the American diet are:

(1) Progressive depletion of much of the soil in current cultivation with the consequent production of nutritionally inferior crops (85).

(2) The increasing use on crops of incredibly toxic insecticides which leave stable and tenacious residues on and in food (7, 17, 30, 31, 33, 34, 40, 41, 49, 65, 68, 70, 76, 89, 106), and at the same time further impair the fertility of the soil by destroying soil microorganisms (91, 106) and earthworms and cumulating to a concentration inhibitory to plant growth (35, 106).

(3) The increasing tendency to pick, ship, process and consume orchard and horticultural produce before it is fully ripe, hence before it has attained its full complement of essential nutrients.

(4) The continuously increasing tendency toward processing (use of detergents, chemicals which promote "keeping," addition of dyes, coating with waxes, heating, etc., etc.) and "purification" (bleaching, decolorizing, and the like) of much of our food (40, 65).

(5) The substitution of virtually pure, vitamin-free sucrose for as much as a fourth to a sixth of the average caloric intake.

1. This is well illustrated in observations on "Kwashiorkor," a "malignant malnutrition" seen thus far primarily in Africa, but also evident elsewhere. This disorder shows "extraordinary resistance to therapy with individual nutrients, whether they be vitamins, lipotropic substances, liver extract, or protein concentrates." Yet whole liver is among the therapeutic agents to which this syndrome shows a favorable response (104).

(6) The use of a variety of chemical additives in food processing, some of which may be toxic and others of which, while apparently harmless, nevertheless displace essential nutrients (40).

Depletion of the soil occurs as a result of many common farm practices, such as failure to rotate crops or to rest the land (39); the year after year use of chemical fertilizers to the exclusion of organic materials (102) (which is analogous to the use of a few synthetic vitamins in human nutrition to the exclusion of complete natural sources); deforestation and similar practices which lead to erosion of the soil; cumulation in the soil of toxic insecticides, fungicides and herbicides, which destroy or inhibit soil microorganisms and directly inhibit plant growth. (For instance, benzene hexachloride, the most widely used of all the current profusion of deadly insecticides, has been found to produce protracted destruction of nitrifying bacteria and other soil microorganisms, without which plant life would soon disappear.) (91)

It has been demonstrated that crops grown on such depleted or toxic soils are nutritionally inferior (85) to those grown on properly cultivated, poison free soils, with their normal complement of organic matter, prime and trace minerals, symbiotic microorganisms, and earthworms, whose contribution to soil fertility so impressed Charles Darwin.

A greater and greater portion of the American diet is depleted by milling, oxidation, heat, chemicals and solvents and by storage. The partial restoration of some of the factors removed by processing, through fortification of bread and cereals with three or four crystalline elements does not begin to make up the total deficit (72).

A further serious depletionary factor arises from the consumption of sugar. It is not generally realized how large a proportion of the total caloric intake is provided by virtually chemically pure, vitamin-free sucrose. The annual consumption of sugar in the United States is in excess of 100 pounds per capita (in 1930 this reached about 118 pounds) (61). This provides approximately 500 calories per day per person or from one-fourth to one-sixth the average total. The requirement for the B vitamins is in direct proportion to the intake of carbohydrate. Thus, in order to burn this sugar, B vitamins must be borrowed from the remainder of the diet which rarely has enough for its own calories. As the requirement for thiamine and riboflavin (the most extensively studied in this respect among the B vitamins) appears to be about 0.5 mg. each per thousand calories, the deficit for these factors alone produced by the intake of sugar, amounts to about 0.25 mg. a day. While various protective mechanisms probably function to prevent the full impact of this depletion, its significance may nevertheless be appreciated by the fact that this would represent a cumulative deficit of approximately 90 mg. of thiamine and riboflavin each in the course of a single year. For niacin, the deficit thus produced would be about ten times this amount. And those who refrain from using sugar in coffee or sprinkling it on cereals and fruit in the belief that the intake is thus reduced to zero, are of course mistaken. Sucrose is incorporated in so many staple foods today, even including bread, that it can hardly be avoided.

But dietary deficiency is only one of a vast number

of causes of nutritional deficiency (4, 64). Numerous studies have indicated that lesions of nutritional deficiency may be produced even in the presence of an adequate diet, by factors which impair absorption of essential nutrients (e.g., gastro-intestinal disturbances, biliary disease) or increase the requirement (e.g., pregnancy and lactation, hyperthyroidism, excessive physical activity, infections), or interfere with utilization (e.g., radiation therapy), or increase destruction (e.g., estrogens, sulfonamides, antibiotics, industrial poisons, inhalation of toxic products such as lead from the polluted air of our large cities and highways, insecticide residues on fruits, vegetables and grain), or increase excretion (e.g., lactation, excessive perspiration, polyuria). Emotional disturbances, especially when they are severe or protracted, or both, can cause extremely marked exacerbations of nutritional lesions. These operate through several of the mechanisms mentioned.

Certainly the combination of all the factors mentioned has led to an incidence of nutritional lesions far greater than is commonly appreciated. Mainly, this is due to failure to recognize avitaminotic disturbances for what they actually are (e.g., cheilosis, glossitis, gingivitis, certain forms of dermatitis, symptoms related to hepatic dysfunction and to disturbances of the nervous system). The author's experience derived from routine Kodachrome photography of patients from all economic strata, over a period of eleven years, and from a survey of a presumably healthy institutional population, derived from a large area of eastern United States, is that gross lesions of nutritional deficiency, easily detectable to the naked eye, are extremely common. For discussions and illustrations of the types and nature of the lesions to be observed, reference is made to these earlier publications (8-14, 16, 18, 20-24).

Tissues once depleted, require much more of the essential factors than it is possible to obtain even in an optimal diet. It is nevertheless important that the diet be as rich in protein and vitamins as feasible. But the vitamin content of the diet may not be depended on to yield quantities sufficient to heal nutritional lesions. Experience indicates that at least ten, twenty, even fifty times the maintenance amounts for persons who have never been deficient, are often necessary for therapy. And even after all the lesions have healed, the maintenance dosage remains at least five to ten times the normal intake indefinitely. The reason for this may perhaps be found in some experiments reported by Bessey and Lowry (5). Reduction in riboflavin intake in the rat led to diminution in riboflavin content of the cornea. But restoration of riboflavin to the diet failed to restore the original riboflavin content of the cornea. Apparently a qualitative change takes place in depleted tissues which no longer permits them to utilize the normal amounts.

Empiricism and Skepticism in the Therapy of Disorders Secondary to Nutritional Deficiency

In previous publications we have demonstrated that a number of endocrine and metabolic disturbances may arise secondary to nutritional impairment of hepatic function. Alterations in the estrogen-androgen equilibrium (owing to failure of the nutritionally-deficient liver to inactivate estrogen) leads to a variety of disorders both in the male and female. Hepatic dysfunction on a nutritional basis may also lead to disturbances in carbohydrate metabolism. Intensive, complete and persistent nutritional therapy has been shown to produce dramatic amelioration of the endocrine and metabolic syndromes. These observations have repeatedly been confirmed by others.

As an unfortunate sequel to these observations there have been numerous attempts to empiricize the necessary nutritional therapy. Many who, for instance, would not think of giving the same dose of insulin to every diabetic, regardless of the severity of diabetic status, demand a "standard" regime of vitamin therapy for these patients, to be applied indiscriminately. It is of course necessary first to assess the condition of the patient on a nutritional basis and to treat him accordingly. The endocrine or other metabolic disturbance secondary to the avitaminosis will of course subside as the nutritional status of the patient improves.

Others, skeptical of the efficacy of nutritional therapy, point out that the amounts of certain of the factors incorporated in the therapeutic regime (e.g., choline) may not be more than is already in the diet. In their zeal to discredit nutritional therapy, these skeptics seem to forget the barest elements of arithmetic. The therapeutic products are not substituted for, but added to, the diet. Even in biology a one hundred per cent increase can usually be considered significant.

Skepticism about and partial acceptance of nutrient therapy reflect themselves also in less obvious ways. Because of the rapidly rising incidence of cardiovascular diseases and the association of atheromatosis with lipoid metabolism, there has been a growing interest in "lipotropic" therapy. Again, as a result of the tradition for the use of single drugs, a great many attempts have been made to treat disordered lipoid metabolism with individual "lipotropic" members of the B complex, or with the single amino acid, methionine. Largely overlooked has been the fact that the defect in fat and steroid metabolism reflects a more general nutritional disturbance. Not only are other, usually quite obvious, nutritional defects invariably associated with the hepatic dysfunction that leads to the lipoid disturbance, but the "lipotropic" effect itself is one shared by a number of nutritional factors, choline, inositol, methionine, vitamin B_{12}, and other as yet unidentified substances known to occur in liver, *all of which are necessary to health and life*. The damaged liver, unable properly to cope with lipoid metabolism, is deficient not only in the known "lipotropic" substances, but in numerous other factors as well, water-soluble, liposoluble and insoluble. Only by providing *all* the missing factors simultaneously can healthy self-regulatory mechanisms be restored.

Importance of Simultaneous Availability of All Essential Nutrients

The vitamins operate in a series of interrelated cellular enzyme systems. Many of them require phosphorylation and association with specific proteins as well as with trace minerals for their normal function. The absence of any one of the numerous essential factors at any one time may seriously disrupt the entire metabolic chain and cause profound disturbances in oxidative metabolism. Complete therapy therefore implies simultaneous availability of *all* essential nutrients.

This is impressively illustrated by investigations on

protein synthesis. Numerous independent studies have shown that unless all the essential amino acids are available at the same time, these substances are irretrievably lost and protein synthesis cannot take place. If, after feeding a mixture containing all but one of the necessary amino acids, the missing substance is not supplied until *three hours* later, there is definite interference with the formation of protein (52).

In fact, it has been found that simultaneous feeding of all the amino acids, nonessential as well as essential, is more effective than feeding the essential ones alone. (This is because, when the "nonessential" amino acids are absent from the diet, the body must manufacture them for the essential acids.) (52)

The water-soluble vitamins are poorly stored even by healthy tissues and storage is even more evanescent after a nutritional defect has once occurred. The oil soluble vitamins are usually well stored by healthy tissues, but are lost readily once a severe deficiency has occurred. This is especially true when severe liver damage has taken place.

Actual clinical practice provides innumerable examples of the superiority of providing all essential nutrients in adequate quantity simultaneously. Thus it is advisable to administer complete vitamin preparations with meals. The latter should of course contain protein of optimum quality in adequate amount. Trace minerals are often lacking in otherwise good diets because of extensive demineralization of much of our artificially fertilized soil. When whole desiccated liver is used as a source of the as yet unidentified but essential nutritional factors, both trace minerals as well as a certain amount of protein of highest quality are simultaneously provided. Although in actual practice it has rarely been necessary to supplement such therapy by addition of further trace minerals, the mineral content of liver products must of course vary from batch to batch and it is not certain that the entire need for all trace minerals can always be supplied by this source. Hence supplementation with these elements may often be advisable.

PRODUCTS AND ADMINISTRATION

Three basic principles of nutritional therapy, repeatedly mentioned elsewhere, may nevertheless be worth reiterating at least once again. Therapy should be *complete, intensive* and *persistent*. Neglect of any one of these three principles leads to ultimate failure, and may even cause deterioration in the nutritional status of the patient.

As already indicated, the various vitamins function in cellular metabolism in a series of enzyme systems, which in simplest analogy, are like links in a chain. Making up these links also are proteins, phosphate, lipoids, and trace minerals. It may appear unnecessary to point out that there is little advantage in strengthening a dozen links in this chain, or even all of them but one, if that one link is weak or broken. Yet current practices in nutritional therapy reveal how poorly understood is this simple fact.

While the range of permissible dosage for essential nutrients is wide owing to the numerous safety mechanisms available to the organism, and the therapeutic range is ordinarily at least five or ten times the range for maintenance and often more, this does not mean that (as is often done) massive doses of certain factors should be combined with minimal doses of others.

The large doses of vitamin A often prescribed, for instance, may precipitate a deficiency of B factors (cf. 56). Conversely, administration of the B complex appears to enhance the utilization of vitamin A and to make such large doses unnecessary.[2] Excessive doses of niacinamide may make it difficult or impossible to heal lesions such as cheilosis, for instance, even though what would otherwise be an adequate dose of riboflavin is included in the regime. In fact the author has frequently observed the actual induction of cheilosis on the "therapeutic formula" type of product containing large doses of niacinamide and vitamin A with smaller proportionate doses of vitamin D, ascorbic acid, thiamine and riboflavin.

As already pointed out, large doses of thiamine alone or in combination with a few other crystalline vitamins are often of little value in the treatment of the neuritis and other manifestations of beri-beri, in which thiamin deficiency is unquestionably implicated, yet the whole B complex causes prompt amelioration of the disorder. Likewise massive doses of niacin or niacinamide are only of temporary benefit in the therapy of pellagra; protracted control of the disease is possible only with the inclusion of an adequate amount of a complete natural source of the B complex. As another example, Vilter and Schreiner (101) have recently reported amelioration of resistant seborrheic dermatitis by local application of pyridoxine. But here too, as they state, "the remission is usually not permanent because the fundamental abnormality is not simple pyridoxine deficiency."

Thus, although the available crystalline vitamins are extremely valuable, the tendency to *excessive* fortification of natural sources is to be deprecated, since the dose is more often than not estimated on the basis of the synthetics present, rather than on the more rational basis of the amount of natural source.

Many available products, with pretentions of completeness, provide massive doses of synthetics and only homeopathic amounts of the unisolated factors. A satisfactory product should provide, in the usually prescribed dose, the equivalent at the very least, of an ounce and a half of a potent natural source, preferably liver, a day and often as much as four or five ounces

2. The protracted and continuous administration of large doses of vitamin A (100,000 to 200,000 units per day) for the treatment of acne, for instance, in the absence of a suitable supplement of the B complex, has been observed to precipitate menorrhagia in a number of our cases. Reduction in dosage of vitamin A not to exceed 50,000 units a day and administration of B complex invariably resulted in subsidence of the menorrhagia (and, incidentally healing of the acne!). A return to the original therapy led to exacerbation of the menstrual disturbance.

In unpublished observations some years ago by the late Dr. J. M. Lewis and the author in animals, estrogen was found to interfere both with blood levels and liver storage of vitamin A despite massive supplementation with the latter. We had previously shown that B complex deficiency leads to failure of inactivation of estrogen in the liver and the development of related clinical syndromes. Thus B complex deficiency alone may indirectly interfere with vitamin A metabolism, and correction of the former obviates the massive doses of vitamin A often used.

calculated to the fresh material. This would represent equivalently less of the desiccated material or extracts.

This, as already indicated, applies as much to so-called "lipotropic" therapy as to other varieties of nutritional supplementation. While the introduction of the term "lipotropic" was helpful in that it served to bypass a considerable prejudice to "vitamin therapy" in general, much confusion was thus engendered. Physicians who believe vitamins belong only in the diet and that the diet can always be depended on to supply them in adequate quantity, nevertheless, have no hesitancy in violating this belief with "lipotropics," for these by some miracle of logic are treated solely as drugs. But choline, inositol, pyridoxine and cyanocobalamine (vitamin B_{12}) are all members of the vitamin B complex and methionine is an amino acid; their use therefore entails "nutritional" therapy. Furthermore other nutritional factors, identified and unidentified, also play a part in lipoid metabolism and the "lipotropic" factors have many other functions beside their role in the degradation, deposition and distribution of neutral fats, phospholipids and cholesterol.

Realization of these facts is important to adequate therapy of nutritional disturbances involving such disorders. The use of large doses of choline, inositol or methionine alone may ultimately actually aggravate the basic nutritional defect. A balanced and complete regime containing moderate doses of these substances together with all the other recognized essential factors and a satisfactory natural source, invariably produces a superior therapeutic result.

In our original observations on the nutritional therapy of certain endocrine and metabolic disturbances (menometrorrhagia, cystic mastitis, premenstrual tension; infertility, gynecomastia, diminished libido and potency in the male; diabetes, hypercholesterolemia and hyperlipemia) related to hepatic dysfunction, in several large series of cases totalling considerably in excess of one thousand, the amounts of the lipotropic factors choline, inositol, vitamin B_{12}, and methionine, were for the most part those present naturally in the liver preparations. Yet both with regard to amelioration of the nutritional lesions and the hepatic dysfunction, with subsidence of the endocrine or metabolic disorders, the results were excellent. Even hypercholesterolemia and hyperlipemia showed striking reductions on such a regime (23). This illustrates further that the proper object of nutritional therapy is treatment of the whole organism with reasonably balanced preparations and not simply a pharmacologic attack on the liver with massive doses of a single substance. In fact, addition of excess amounts of the lipotropic factors to the type or regime we have used, in some cases actually has led to exacerbation of the original disorder (with subsidence on reverting to the original therapy). Liver preparations, especially desiccated liver, are by themselves a rich source of the lipotropic substances. In our experience the addition of larger amounts of the lipotropic factors (e.g., choline, one gram per day)[3] in patients with severe hepatomegaly and other signs of serious hepatic impairment, does in these cases provide additional benefit, but only when employed together with an otherwise complete regime. The large doses (e.g., choline 4 Gm. per day) often used, we have found neither necessary nor advisable.

Depending on the original nutritional status and response of the patient, adequate nutritional therapy might require 3 tablets or capsules a day of a preparation which provides per dose, vitamin A 10,000 units, vitamin D 500 to 1,000 units, vitamin E 10 to 15 mg., thiamine 10 mg., riboflavin 5 mg., pyridoxine 1 mg., pantothenic acid 5 mg., niacinamide 50 mg., ascorbic acid 100 mg.

For a source of the indispensable *natural source* three types of preparations are especially valuable: (1) Desiccated whole liver, fortified with B vitamins or unfortified, usually at least 9 Gm. (eighteen 0.5 Gm. capsules or tablets) per day. (2) Nutritional extracts of liver fortified with B vitamins, usually 9 or 12 capsules or equivalent amount of liquid per day. (3) Preparations of the types described fortified with larger amounts of choline, inositol, vitamin B_{12} and methionine. All these preparations, for reasons already described, should be given with meals. It is important to make certain that the diet contains adequate protein, since in protein depletion the B vitamins cannot adequately function.

Patients with impaired absorption require parenteral therapy with the crystalline B vitamins, *in addition*, with a frequency ranging from daily to three times a week. Often the latter can be discontinued after the patient is in nutritional equilibrium. For parenteral therapy a mixture may be administered containing from 10 to 50 mg. thiamine, 5 to 10 mg. riboflavin, 5 to 10 mg. pyridoxine, 10 to 50 mg. panthenol or calcium pantothenate and 50 to 100 mg. niacinamide, and when necessary 50 or 100 mg. ascorbic acid. While this dosage may be given in 2 cc., less irritation results if greater dilution is used. In some preparations greater amounts of niacinamide are included, not because they are ordinarily advisable therapeutically, but because niacinamide helps to keep riboflavin in solution. These preparations are otherwise useful and may be divided into two or sometimes three doses.

As everyone with even moderate experience in the use of these preparations has observed, occasional patients may show more or less severe systemic reactions to injection of these mixtures. These include a feeling of warmth, fullness in the head or light headedness, and discomfort in the epigastrium. Occasionally bradycardia and syncope may ensue. These reactions are most likely to occur in severely deficient patients who have symptoms referable to the central nervous system. The reactions are much more common when the injection is made intravenously than when made intramuscularly. In our experience these reactions can be avoided or minimized by taking the following precautions: (1) The patient should always be recumbent during the injection and for a short time afterward. (2) Reactions are less likely to occur if severely deficient patients are first put on intensive oral therapy for a week or so, even if this is not adequate to control the symptoms. (3) Injections should never be made intravenously—the water soluble factors are very rapidly (even too rapidly) absorbed from the muscle. (4) Injections should be made in the upper outer quad-

3. This refers to free choline. It should be kept in mind that the amounts of choline in the commercial preparations are often stated in terms of the dihydrogen citrate. 1 Gm. choline = 2.5 Gm. choline dihydrogen citrate.

rant of the gluteus or deep in the outer aspect of the thigh (*never* in the deltoid), preferably with a no. 22 gauge, 1¼ inch needle, changing the site for each injection. (5) The plunger of the syringe should of course always be withdrawn to make sure no vessel has been entered. (6) The fluid must be injected *slowly*, at a rate not exceeding ½ to 1 cc. per minute, watching the patient for any sign of reaction during the injection and discontinuing if any ensues. (7) After the injection, the needle should be withdrawn rapidly while maintaining pressure with gauze or cotton on the skin around the needle and continuing this pressure for several minutes afterward. Occasionally a vessel may be transfixed and unless pressure over the site is maintained, rapid backflow along the needle tract may simulate the effects of a rapid intravenous injection. Pressure on the site of injection also avoids the painful hematomas so common with this type of therapy.

These precautions may seem troublesome and time consuming at first reading, yet with a little experience they become automatic.

The question of parenteral liver therapy has already been considered. In addition to the low potency of the available preparations (B_{12} excepted) the possibility of sensitization must be kept in mind. Anaphylactoid reactions to liver are fairly common and can be very severe. Sensitization may subsequently interfere with administration of liver or liver products by mouth.

The question of inclusion of folic acid in parenteral preparations is an important one. The author and G. R. Biskind some years ago each observed independently (unpublished observations) that in certain patients in whom menorrhagia, cystic mastitis and related disorders had been under excellent control with the type of nutritional therapy mentioned, inclusion of parenteral folic acid in the regime led to marked exacerbation of the disorders. A male patient under similar therapy developed gynecomastia when parenteral folic acid was instituted. The menstrual disorders subsided and the gynecomastia disappeared when the folic acid was omitted from the injectable therapy. Folic acid *by mouth* was never observed to cause an exacerbation. Hertz and Sebrell (60) have shown in animals that folic acid increases the response of end organs to estrogen; Frost and Dann (51) showed parenteral folic acid to be considerably more effective than oral on growth and feathering of birds.[4] Our observations therefore suggested that on oral administration something happened to folic acid in the portal circulation which prevented this effect, whereas on parenteral administration the folic acid could by-pass the liver and reach the uterus and breasts unchanged. Recent observations (43, 78) have indeed shown that folic acid may be converted in the liver to folinic acid (the so-called "citrovorum factor") although whether this is responsible for the phenomenon has not yet been determined. Because of the responses to parenteral folic acid we have avoided its use by this route and have confined its administration to the oral route.

Choline is another of the B vitamins metabolized in the liver. On oral administration it is thus prevented from exerting its "cholinergic" effect on the autonomic nervous system. However, on parenteral administration (sometimes employed in the treatment of severe hepatic cirrhosis) more or less severe parasympathomimetic effects may ensue. More experience will ultimately determine whether there is a real need for parenteral solutions containing choline. But if they are used at all, they should always be injected very slowly in diluted form, preferably in infusion fluid. Even with this precaution the patient should be under constant observation both during the administration and for some time afterward, so that the infusion may be stopped if necessary, and any late untoward reactions may be treated immediately (the pharmacologic antidote is atropine).

Patients who have been exposed to any of the organic phosphorus insecticides (e.g., parathion, tetraethyl pyrophosphate or "TEPP," hexaethyl tetraphosphate or "HETP") very widely used in agriculture, which cumulatively and irreversibly inhibit cholinesterase, may have enough of the much more active free acetylcholine (although this may be insufficient in quantity by itself to produce symptoms) to contribute to the autonomic effects of the injected choline. It might then be prudent to determine the cholinesterase level of the blood before administering choline parenterally.[5]

FACTORS WHICH INTERFERE WITH THERAPY

It has already been pointed out that nutritional deficiency can be produced by a variety of factors other than dietary depletion. Although this concept has been gaining increasing acceptance, it is not yet generally understood that, if these factors continue to operate during therapy they may be powerful enough partially or totally to defeat the most potent nutritional regime it is possible to apply in practice.

Thus, a person continually exposed to a hepatotoxin, such as one of the industrial solvents or one of the new chlorinated hydrocarbon insecticides, can expect at best only partial relief so long as the inciting agent continues to act. A patient who persists in consuming vast quantities of sugar and other refined carbohydrates, to the detriment of protein intake, can similarly expect little benefit from nutritional therapy. Likewise, an individual under the stress of acute anxiety, which impairs absorption and utilization and increases destruction and excretion of the essential nutrients, will not respond even to massive doses of these substances

4. It is of interest in this connection that on parenteral administration, folic acid is much more toxic to female than to male animals (96).

5. The organic phosphorus insecticides (related to the "nerve poisons" of chemical warfare) may contaminate many food products in amounts capable of producing subacute poisoning. In addition, direct exposure to this agent is common and subclinical cases unquestionably exceed in number the acute poisonings, of which "As many as 30 cases have been reported in California alone in one month . . ."

"Cases of poisoning are by no means limited to persons handling organic phosphate materials. Among those in whom poisoning may be suspected are all agricultural (including greenhouse and nursery) workers who have occasion to enter treated areas, children playing in treated areas, bee keepers, casual trespassers, occupants of houses in or adjacent to treated areas, travelers passing fields during application, mechanics working on contaminated equipment, and many others." (Physicians' Occupational Health Bulletin No. 6, California Bureau of Adult Health, Berkeley, Jan. 1952).

so long as the emotional disturbance continues to act. We have repeatedly observed in many different patients and over and over again in the same patients, that anxiety causes rapid exacerbation of nutritional lesions and development of new ones, despite concurrent intensive nutritional therapy which previously was adequate. On subsidence of the emotional conflict rapid healing ensues.

At first sight, so profound an effect of emotional conflict seems surprising. Yet consideration of the known manifestations of such disturbances reveals several simultaneously operating mechanisms which may interfere with cellular metabolism. Impairment of appetite, perversions of appetite, gastro-intestinal spasm, diarrhea, peripheral ischemia, polyuria, wakefulness, increased metabolic rate, protracted muscular tension, are all factors which secondarily can impair intake, absorption and distribution of essential nutrients to the tissues, increase the requirement and increase excretion.

The list of chemicals and drugs which impair cellular enzyme systems and produce tissue anoxia is very long indeed. An incredible number of them are in such indiscriminate use that daily exposure to them is almost unavoidable for many persons. These range from a variety of chemicals used in industry (54), to carbon monoxide, lead and other products of combustion in automobile exhaust (18),[6] the chlorinated cyclic hydrocarbon insecticides (DDT, lindane, chlordane and the like) (7, 15-18, 30-35, 40, 49, 62, 63, 65, 66, 68-71, 75, 76, 79, 82, 84, 89, 106) which are extensively used in agriculture,[7] public health applications, institutions and homes, paint solvents,[8] and drugs such as sulfonamides, antibiotics and estrogens.

Danziger (38) has compiled a formidable list of chemicals and drugs in common use which are known to cause cellular anoxia. As more substances are studied this list will undoubtedly be greatly expanded. Anoxia causes dephosphorylation of B vitamins, loss of both the vitamins (55) and phosphate (77) from the tissues and their excretion in the urine. Thus, continuing exposure to these substances during therapy may be an insuperable impediment to a satisfactory nutritional response. This one factor, more often overlooked than not, is responsible for many of the failures attributed to nutritional therapy and for many resultant erroneous claims that certain clinical entities of avitaminotic origin are not even related to nutritional deficiency.

This impediment applies as well to a great deal of current nutritional research in animals. For instance, Laug and his associates (68-70) of the Federal Food and Drug Administration, and others have shown that even the faintest trace of DDT (less than 0.1 part per million) and certain related compounds (e.g., chlordane) in the diet are cumulatively stored in the body fat of animals. Laug has called the body fat a "biological magnifier" of DDT. This substance is known to interfere markedly with cellular oxidation (62, 63, 84) and to cause morphologic damage to virtually every organ in the body (15, 17). Yet, in current nutritional research this problem is almost completely ignored. No attempts are made to analyze the basic diets for their content of these substances nor to remove them when present. (It is currently almost impossible to obtain a stock diet free of these substances without the most rigorous precautions.) (7, 17, 19, 34, 40, 41, 65, 68, 75, 79, 82).

Observations on the storage of DDT in human body fat and its excretion in mother's milk, in all series of cases studied from many parts of the United States, indicate that only a small fraction of the population has thus far escaped such storage (17, 19, 63, 70, 75, 79, 82, 89). DDT is known to inhibit heart muscle cytochrome oxidase, for instance, in extremely low amounts (63); it can be seen then that this one factor alone may cause serious initial ailments. And because the tissue storage is tenacious (89) and exposure universal, it also causes serious interference with attempts at correction of the basic enzymatic disturbances.

The widespread use of sulfonamides and even more, antibiotics, is also responsible for a good deal of nutritional impairment. All these substances produce avitaminoses, which complicate the nutritional depletion that may be produced by the infection they are used to treat. Many physicians feel that the vitamins are contraindicated during therapy with these substances, as they are presumed to neutralize in some measure, the bacteriostatic effect of the drugs. The latter effect is however much less important than the fact that recovery cannot ensue unless this bacteriostatic effect is supplemented by the immune bodies produced by the host. Vitamins A and D, the B vitamins, ascorbic acid, and essential amino acids, are all necessary to the production of these immune bodies (2, 26, 29, 42, 53, 73, 105). Yet the antibacterial drug itself causes depletion of these essential factors! (36, 37, 80, 87, 88, 90, 95, 98, 100).[9] It is reassuring however to note that one manufacturer of a widely used antibiotic advocates the *simultaneous* administration of the B vitamins with

6. Exposure to concentrated traffic fumes on highways or city streets has been observed repeatedly to produce rapid and often severe aggravation of glossitis and other signs of avitaminosis despite intensive therapy previously adequate. In heavy traffic, the low ventilator intakes on almost all current makes of automobiles can scoop up only slightly diluted exhaust from the car ahead. (As a cause of accidents the carbon monoxide poisoning thus produced has been largely overlooked.)

7. In agriculture alone, "An estimated 232 million pounds of seven of the principle insecticides (technical grades) were used in 1950:" (Report of the Chief of the Bureau of Entomology and Plant Quarantine, 1951, U. S. Department of Agriculture). Considered in relation to another report issued by the U. S. Department of Agriculture at almost the same time (Toxicity of Insecticides, Fungicides and Herbicides. A Report of Current Research and Research Needs, Oct. 1951) the magnitude of this problem in relation to the public health takes on appalling significance.

8. In studies on the relation of avitaminosis B to the etiology and therapy of menorrhagia and cystic mastitis, the author has noted that severe menometrorrhagia or cystic mastitis, or both, may follow exposure to evaporating paint solvents following redecorating of walls in the home. In two cases severe metrorrhagia thus occurred in postmenopausal women; in twelve others, severe exacerbation of the menstrual disorders followed such exposure despite concomitant nutritional therapy that previously had been adequate. The menstrual disorders subsided gradually only when exposure to the solvents was discontinued.

9. We have observed denudation of the lingual surface in less than 24 hours from the local use of relatively small doses of aureomycin, for instance, in troche form. Usually weeks of intensive nutritional therapy thereafter are required to heal the glossitis thus induced.

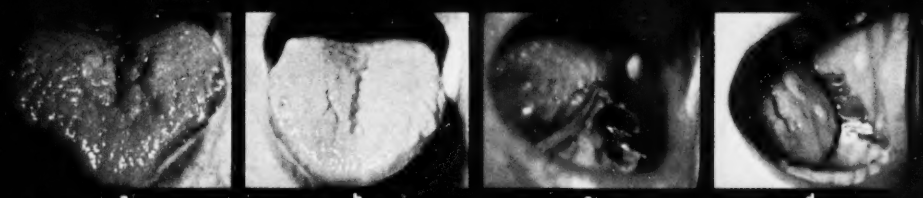

Fig. 1 — **a**, Atrophic glossitis and **c**, thickened, circular leukoplakial buccal lesion in a patient recovering from severe acute hepatitis (diagnosed "infectious" which followed intensive daily inhalational and dermal exposure to DDT from its use about the home. He had been treated with crystalline liposoluble and water soluble vitamins alone, for 3 months, without improvement in the oral lesions. **b** and **d**, Healing of glossitis and buccal lesion after 8 months on a complete regime containing crystalline vitamins plus large amounts of desiccated liver.

Fig. 2 — **a**, Leukoplakia at angle of lips and adjacent buccal mucosa in a diabetic unresponsive to treatment with 3 capsules a day of a therapeutic vitamin formula preparation. Note folding of thickened epithelium. **b**, Noticeable healing of leukoplakia after 2 months on a combination of crystalline vitamins and desiccated liver. (See reference 16, case 3.)

Fig. 3 — **a**, Severe desquamative, hemorrhagic gingivitis treated without improvement for more than a year with vitamin A, ascorbic acid and a variety of elimination diets. **b**, Improvement after 2 months on a complete regime including desiccated liver and a full diet. The lesions were completely healed 4 months later.

Fig. 4 — **a**, Cheilosis produced by administration of a therapeutic vitamin formula preparation. **b**, Almost complete healing of cheilosis 1 month later after adding desiccated liver to this regime.

Fig. 5 — Cheilosis produced by administration of niacin.

Fig. 6 — Exacerbation of glossitis despite continuation of intensive complete nutritional therapy, following bronchopneumonia treated with 3 million units of penicillin (same patient as Fig. 7).

Fig. 7 — **a**, Initial glossitis refractory to a variety of combinations of crystalline vitamins, yeast and yeast extracts, rice bran extract, and oral and parenteral antianemic liver extracts. **b**, Complete healing of glossitis on a combination of crystalline vitamins orally and parenterally, and daily ingestion of cooked whole liver. **c**, Severe exacerbation of glossitis during acute anxiety despite continuation of intensive therapy previously effective in **b**. **d**, Healing of all but left anterior portion of tongue after subsidence of acute anxiety. (Fig. 6 chronologically followed 7d.)

the antibiotic. And of course vitamin therapy must be continued for some time after the antibacterial therapy has been discontinued, to make up the remaining deficit.

Careful questioning of the patient as to direct or indirect exposure to chemicals and drugs known to interfere with enzymatic oxidation, is often of paramount importance to successful nutritional therapy. An example of such exposure rarely suspected by patient or physician is the ingestion of stilbestrol from its agricultural use in caponizing and fattening (with tissue water retention) poultry (and to an increasing extent, other farm animals). Not only is it often possible to ingest the remains of the original 15 mg. pellet implanted in the neck of the animal, but enough stilbestrol is present in the meat and liver of the animal to produce therapeutic effects (40, 44, 57, 59). Another widespread uncontrolled use of stilbestrol and other estrogens is in cosmetics. The estrogens are now known to use up the B vitamins in their detoxification in the liver (1, 8, 9, 11, 20), hence can produce lesions of avitaminosis and exacerbation of those already present. This too may occur despite nutritional therapy previously adequate.

* * *

It is obvious from the foregoing that the concept of specificity, so prevalent in the philosophy of modern therapeutics, cannot successfully be applied to nutrition, experimental or clinical. The nutritional needs of the organism reflect the basic complexities of cellular metabolism, which are of surpassing intricacy. Restoration of healthy self-regulatory mechanisms should be the primary aim of nutritional therapy. This can only be accomplished by supplying simultaneously *all* the necessary macro- and micronutrients in sufficiently intensive but not excessive amounts and in reasonable proportion. Nutritional products of modern chemistry are highly useful in this endeavor but at the present state of technology they can only *supplement* and not replace complete natural sources of nutrients.

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TRANSPYLORIC PROLAPSE OF GASTRIC MUCOSA

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PROLAPSE OF gastric mucosa through the pyloric canal is the result of hypertrophic gastritis of the antral mucosa. The hypertrophied rugae are forced into the pylorus by gastric peristalsis and may produce varying degrees of obstruction. The clinical picture, therefore, is that of chronic gastritis upon which are superimposed the symptoms of an inconstant pyloric obstruction. This combination of symptoms is suggestive of peptic ulcer, and many of these patients are so considered and so treated.

The radiologic appearance of the lesion is inconstant. It varies with the amount of mucosa prolapsed and with the degree of obstruction produced. When a moderate amount of mucosa has prolapsed through a relatively normal pylorus, a filling defect is produced in the base of the duodenal cap. This has been described as the "toadstool" or "umbrella" sign and is considered to be pathognomonic when present (Fig. 1). It is possible, however, to have such a high degree of obstruction, due to complete filling of the pyloric canal with prolapsed mucosa, that the duodenal cap will not visualize. In this instance the pyloric antrum has a pinched off appearance which might be called a "funnel" sign (Fig. 2). A third radiographic picture is formed when compensatory dilatation of the pyloric canal occurs as a result of stretching of the Sphincter muscle. This results in the prolapse of relatively large amounts of antral mucosa into the duodenum. The roentgenogram in this instance shows a dilated pylorus with evidence of gastric rugal pattern extending into the base of the duodenal cap (Fig. 3). This type of picture is often seen in individuals who are asymptomatic.

The difficulty of establishing the correct diagnosis is a burden not only for the internist and radiologist. It is possible for the surgeon to overlook the condition even at laparotomy. Palpation of the pylorus is inconclusive; although the hypertrophied mucosal folds are palpable as a vaguely outlined thickening in the antrum, it is usually difficult to decide whether or not it really

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Fig. 1: A roentgenogram of the pylorus showing the typical "toadstool" or "umbrella" sign of prolapsed gastric mucosa (Case No. 1).

represents pathology. When a dilated pyloric muscle is present, it offers an excellent indication for gastrotomy. A dilated pylorus in the absence of duodenal obstruction is almost certainly due to prolapse of a gastric polyp or of antral mucosa. Slight thickening palpable in an otherwise normal appearing antrum and in the absence of other pathology is sufficient evidence to do a gastrotomy for confirmation of the diagnosis.

The treatment of the condition should be kept as simple as possible. A trial of medical management is in order. If this does not afford relief, or if symptoms progress, laparotomy should be resorted to. The usual course of events is for the patient to undergo medical treatment for vague epigastric distress until an upper G. I. series is done. The findings of the radiologist are frequently misinterpreted; a malignant lesion is often suspected and laparotomy is recommended. In the face of such a story the surgeon is well advised to palpate the pyloric antrum most carefully—especially if he finds it to be normal in appearance. A gastric resection is not indicated for prolapse of gastric mucosa and should be avoided. When doubt exists, the best procedure to do is a 2 cm. gastrotomy in the anterior surface of the pyloric antrum immediately orad to the pylorus. If the symptoms are due to transpyloric prolapse of the gastric mucosa, the offending, hypertrophic rugal folds will be easily demonstrable. With the diagnosis established the gastrotomy incision can then be lengthened caudad to transect the pyloric muscle, and the defect can be closed transversely (Heineke-Mikulicz pyloroplasty). This is a relatively minor surgical procedure which relieves the obstructive symptoms with a minimum derangement of gastrointestinal physiology.

CASE REPORTS

Case No. 1, H. E. R.—A 39-year-old white male patient was admitted to the hospital for the treatment of headache, chills and fever accompanied by vomiting and epigastric discomfort. Although his fever subsided, the nausea and vomiting persisted, and at time of admission he was unable to retain either liquids or solids. He said that he had been treated for duodenal ulcer for the past seven years. His symptoms were recurrent, and he had been hospitalized several times for treatment.

Physical examination revealed a well-nourished and well-developed adult male of the stated age who was apparently suffering with severe abdominal pain, lying in bed with his knees flexed on his abdomen. He was vomiting at the time of examination, and there was marked tenderness in the mid-epigastrium. The liver was tender on percussion, and its edge was palpable at the costal margin on deep inspiration. There was no muscular rigidity and no distention. The laboratory data revealed a leucocytosis of 13,700; 4.67 million red cells and 16.1 grams of hemoglobin. The urinalysis and serology were negative. The serum amylase was 81 mg. percent, and a gastric analysis revealed 59 units total acidity. A flat plate of the abdomen revealed no pathology, and a routine chest plate was normal. A G. I. series did not suggest any specific pathology to the radiologist. The umbrella sign, however, could be demonstrated in retrospect (Fig. 1).

Fig. 2: Almost complete pyloric obstruction, indicated by the "funnel" sign, due to prolapse of gastric mucosa (Case No. 2).

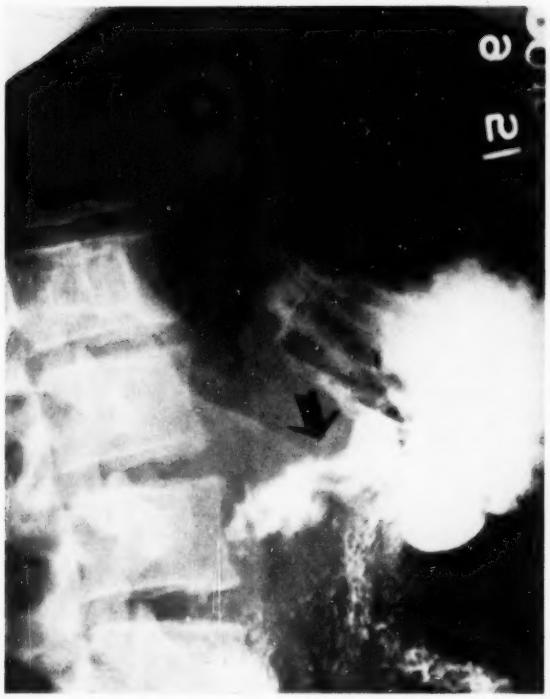

Fig. 3: Transpyloric prolapse of massive amounts of gastric mucosa carrying the gastric rugal pattern into the pyloric canal. Note the longitudinal striations in the pyloric canal (Case No. 3). The gastric rugal pattern is accentuated throughout the stomach.

Because of the pyloric obstruction and the history of chronic duodenal ulcer he was subjected to a laparotomy. At operation the abdominal exploration was negative with the exception of a questionable amount of thickening in the region of the pylorus. A gastrotomy was felt to be indicated, and a longitudinal incision was made through the pylorus extending for approximately 1 cm. into the duodenum and 1 cm. into the antrum. When the incision was opened, it became quite obvious that the obstruction was due to hypertrophic gastric mucosa which could be demonstrated hanging through the pylorus. A Heineke-Mikulicz pyloroplasty was done. The postoperative course was completely uneventful, and symptomatic relief was complete.

Case No. 2, J. C. T.—A 57-year-old white male admitted to the hospital for treatment of an undiagnosed intestinal condition. He gave a rather incoherent story of abdominal difficulties of two years duration which began with an emotional upset occasioned by the death of his wife, brother and father within a period of eight months. His chief complaint was recurrent epigastric pain occurring most commonly toward evening and usually right after a meal. The pain was described as a dull ache localized to the mid-epigastric region. Occasionally he had obtained relief from the pain by vomiting. There had been a weight loss of 45 pounds in the past two years.

Physical examination revealed a well-developed, under-nourished white male of the stated age who was ambulant and appeared chronically ill. Physical examination was not particularly helpful. The abdomen was scaphoid, and high in the mid-epigastrium was an area of tenderness. The laboratory data revealed a normal urinalysis and serology; a leucocytosis of 14,000; a red count of 5.04 million, and a hemoglobin of 14.6 gms. A gastric analysis revealed a total acidity of 96° and 82° of free acid. A routine x-ray of the chest revealed no significant disease. The gallbladder visualized and emptied normally. A G. I. series was reported as discovering an ulcerated lesion of the antrum with a question of carcinoma. These x-rays were repeated and reported as, "Spasm and deformity about the pyloric antrum. . . . a definite conclusion regarding the question of neoplasm cannot be made at this time. I believe there is definite ulceration and that it is on the gastric side of the pylorus. I believe that there is still a strong possibility of malignancy. . . ."

Because of a possible gastric malignancy the patient was prepared for operation. At laparotomy, exploration revealed a fibrous thickening of the pancreas; careful examination of the gland revealed no tumor nodules. The pylorus of the stomach was found to be somewhat thickened, and there was scarring of the first portion of the duodenum indicating an old healed ulcer. The thickening in the region of the pyloric antrum could not be definitely interpreted by palpation, but because of the evidence of duodenal ulceration a gastric resection was decided to be indicated. An anterior isoperistaltic Polya type of anastomosis was done. Examination of the gross specimen of stomach revealed the pathology to be a ring of gastric mucosa which was prolapsed through the pylorus. The prolapsed mucosa was found to be hyperemic, thickened and formed a pseudovalve approximately 1 cm. long (Fig. 4). The histopathology showed atrophy and thinning of the mucosa with a heavy infiltration of lymphocytes (Fig. 5).

Case No. 3, H. C. H.—A 57-year-old white male was admitted to the hospital for treatment of a peptic ulcer. He complained of epigastric distress of three years duration. This usually came on one or two hours after eating and especially after the noon meal. It was described as usually being a feeling of hunger

Fig. 4: The gross appearance of prolapsed gastric mucosa in a section of stomach resected for duodenal ulcer (Case No. 2). The arrow indicates the hyperemic fold of mucosa which was obstructing the pylorus.

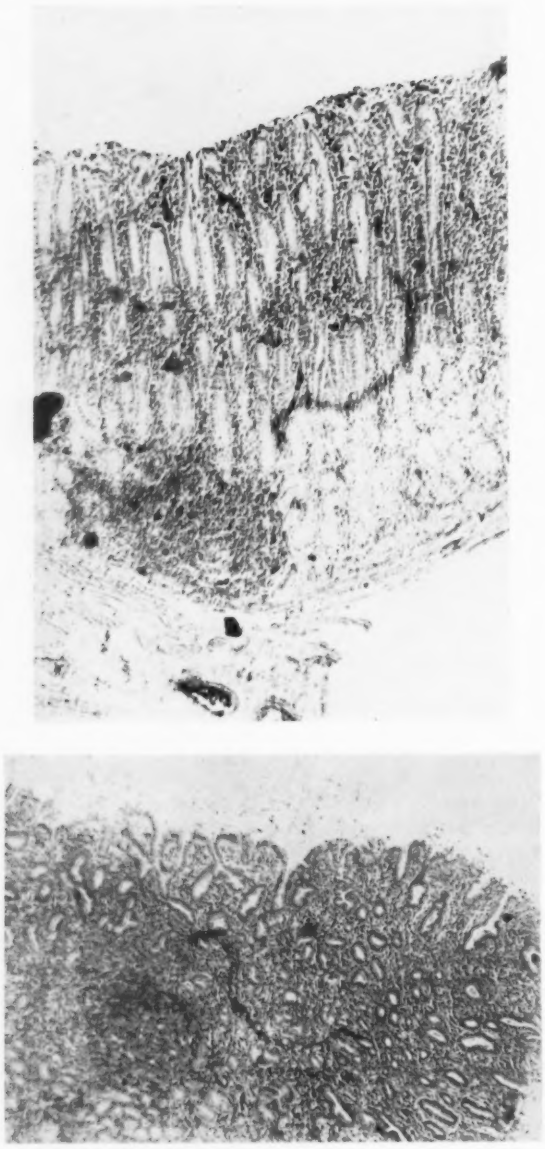

Fig. 5: Photomicrographs of the prolapsed mucosa of Cases 2 and 3. There is considerable polymorphonuclear infiltration but no ulceration. Lymphocytes are abundant also and are forming germinal centers.

but occasionally as a sharp pain. Milk and antacids always seemed to relieve his distress.

On physical examination a well-developed, well-nourished, tall and rather thin patient was described. There were no unusual findings elicited; the abdomen was flat and non-tender. The laboratory examinations were within normal limits with the exception of a G. I. series which showed coarsening of the rugal pattern of the stomach. A gastroscopic examination confirmed the presence of hypertrophic gastritis. He was placed on a Sippy regimen, became symptom free and was discharged with advice to continue his ulcer treatment.

He was readmitted about a month later, having had a recurrence of the pain. Another G. I. series suggested the presence of a gastric ulcer which was reported as ". . . questionable ulcer middle third, lesser curvature of stomach. Marked hypertrophy of the gastric mucosa."

Because of the persistence of a gastric ulcer the patient was subjected to laparotomy. Exploration of the abdomen was completely negative with the exception of some polyps in the sigmoid colon and a dilated pylorus. Careful examination of the duodenum failed to reveal an obstruction or other cause for dilatation of the pyloric ring. A soft, vaguely outlined mass was palpable in the pyloric antrum which could be prolapsed through the dilated pyloric ring by manipulation. It was thought that this might be a polyp, and therefore the pylorus was opened by means of a longitudinal incision. This revealed large, hypertrophic, gastric rugae which could be demonstrated prolapsing through the pyloric canal. A biopsy of the mucosa was taken, and the longitudinal incision was closed transversely (Heineke-Mikulicz pyloroplasty). Treatment of the sigmoid polyps was deferred because the bowel had not been prepared for resection.

The histopathology of the mucosal biopsy was as follows: "These sections show a covering of this tissue with a reasonably normal appearing gastric type mucosa. The muscularis mucosa is present in the central portion of the polypoid mass and is partially infiltrated with lymphocytes. There are focal areas of collections of lymphoid tissue into the germinal follicle pattern. Through the mucosa there is a scattered polymorphonuclear cell infiltration which in some areas is reasonably intent. The epithelium lining the glands is quite normal in appearance. (Fig. 5).

DISCUSSION

Transpyloric prolapse of gastric mucosa is regarded by some as a physiological variant of the normal. Most clinicians, however, feel that at least in some cases symptoms are produced by prolapsing gastric mucosa. In the cases here reported it would be difficult to say that the symptoms were not produced by the prolapsed mucosa since relief after operation was so positive.

There is undoubtedly a pronounced personal variation in the interpretation of the radiological examination. In our experience the diagnosis is rarely if ever made by the radiologist. Confusion of the radiologic findings with those of cancer brought our cases to laparotomy. The diagnosis was made at gastrotomy, and the roentgenograms were correctly interpreted in retrospect. From this one could deduce that a radiologic diagnosis alone, of prolapse of the gastric mucosa, is insufficient evidence for surgical exploration. If exploration is indicated because of symptoms, the surgical procedure should be as simple as possible. Mutilating operations are to be avoided. A procedure such as the Heineke-Mikulicz pyloroplasty is adequate. By enlarging the pyloric canal and dividing the muscle it relieves the obstruction and prevents strangulation. The treatment of the accompanying gastritis is medical.

SUMMARY

The importance of transpyloric prolapse of gastric mucosa as a source of symptoms is reviewed. The difficulties encountered in arriving at this diagnosis are de-

scribed. Mutilating operations are not felt to be indicated. Three cases are reported.

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AN UNDERSTANDING OF PROLAPSED GASTRIC MUCOSA

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FEW DISEASES of the gastrointestinal tract have occasioned more controversy than has the relatively recently described condition of prolapsed gastric mucosa into the duodenum. Autopsy (1) and surgical (2, 3, 4) findings, in addition to the characteristic x-ray findings (5, 6), leave no doubt as to the actual anatomical entity; but the clinical significance of such herniated folds poses quite a problem.

THE NATURE OF THE DISEASE

The first factor in the understanding of this disease is the realization of just what the disease represents. For practical purposes the prolapsed gastric folds represent nothing more than herniated gastric folds into the duodenal bulb. These may vary from single to multiple folds or even to a prolapse of the circumference of the stomach in the antral area. Regardless of the etiology, and the causes are undoubtedly multiple, the condition results when any mass, whether it be an enlarged or displaced rugal fold or even a neoplasm (15), is presented at the pyloric canal and passes through it. The gastric hyperperistalsis consistently associated with prolapsed gastric mucosa may be primary or secondary. The primary type occurs in those individuals whose psychogenic gastrointestinal disturbances result in their having gastrointestinal hypermotility in general. In these individuals, the gastric hypermotility probably precedes the prolapse, and is a definite aggravating factor in the production of the disease. In the secondary type the hypermotility probably was not present before the prolapse was established, and in these individuals it is probably a compensatory mechanism to propel the gastric contents past the variable degree of pyloric canal obstruction resulting from the presence of the gastric folds in the canal.

As is true of any hernia, this herniation of gastric folds may be reducible or non-reducible. Complete or relative reduction of the herniation probably can result from external pressure (6, 7), from reduction in edema of the prolapsing folds (1) and from reduction in the degree of congestion or inflammation of the folds (7, 8). Aggravating factors include edema (1) of the gastric mucosa, gastritis (8), the occasionally reduced lumen of the pyloric canal (2) and gastric hyperperistalsis (5, 6, 14); and amelioration of one or more of these tends toward spontaneous reduction of the herniation. On the other hand, little or no reduction in the degree of prolapse can be anticipated if the basic etiological factor or factors are not materially corrected or if the volume of the herniated folds be great, as was case No. 5 reported by Patterson and his associates (9).

To consider such a condition a physiological variant of normal (10) is the equivalent of considering an inguinal hernia to be physiological.

SIGNS AND SYMPTOMS

The signs and symptoms of prolapsed gastric mucosa have been carefully observed and reported by numerous authors (5, 6, 11, 14), but a brief discussion of the cause and significance of such is in order. Vomiting is a rather frequent finding in patients presenting prolapse of the gastric mucosa. Fluoroscopic findings in these patients tend to rule out reversed gastric gradients (12) as a cause. The most probable cause is a relative blockage of the pyloric canal by the herniated folds, possibly aggravated by some degree of pylorospasm. Reduction in the "swelling" of the folds, reduction in the degree of pylorospasm (by anti-spasmodics, sedation, psychotherapy, etc.) or the regular ingestion of soft foods which pass such a block easier tend to reduce the degree of obstruction and thus reduce or stop vomiting.

If there is a break in the mucosa of the prolapsed folds, the action of hydrochloric acid on the defect will give pain the same as it would were the fold in its normal position in the stomach. Should the break in the continuity of the mucosa be of such location anatomically as to involve blood vessels, bleeding can result readily; and no doubt bleeding is encouraged by the relative interference with venous return to the base of the fold as the result of pressure imposed by the pyloric canal.

Most workers analyzing the symptoms associated with prolapsed gastric mucosa have been impressed by the vagueness and the inconstant pattern of the symptoms. This is not unduly remarkable when one considers that diseases of the gastrointestinal tract in general are notorious for their vague and indefinite symptoms. The stomach, in which even carcinoma may be silent until it is far advanced or in which peptic ulceration tends to be more vague symptomatically than when it is present in the duodenum, is the site of origin of the prolapsed folds and so is the source of innervation. Thus it is not surprising that the symptoms of prolapse tend to be vague and of no definite

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pattern. At times the prolapse may be entirely asymptomatic (7). Not infrequently the symptoms attributed to prolapsed gastric mucosa probably result from associated diseases. Bralow and his associates (13) recently have reemphasized the frequent association of duodenal ulcer with prolapse of the gastric mucosa, and likely the crater of duodenal ulcer is frequently masked by the presence of the prolapse. Most workers (8, 13, 14) reporting analytical studies of prolapse of the gastric mucosa have been impressed with the frequent co-existence of gastritis. Such a combination is particularly difficult to evaluate; because gastritis itself is still the subject of controversy so far as symptomatology is concerned. Another point to emphasize is that prolapse at times may well represent a permanent or transitory phase in the pathogenesis or healing of duodenal ulcer in certain given cases (7, 13). Finally, prolapse of the gastric mucosa may be transitory at times (7) and this factor may cause considerable confusion in the mind of the worker analyzing cases.

CRITERIA FOR DIAGNOSIS

Since the symptomatology of prolapsed gastric mucosa is so irregular as to preclude any significant frequence of clinical diagnosis, x-ray remains the only non-surgical method of making a definite diagnosis. This method, too, is a stumbling block if rigid criteria are not observed. Failure to adhere to these criteria is probably the greatest factor in explaining why a few authors report an excessively high percentage of incidence of prolapse or an excessively high percent of asymptomatic cases. Such minor aberrations as a slight indentation of the base of the duodenal bulb does not represent a prolapse, although some consider it such; in fact such a deformity can be produced frequently in normal individuals by such simple methods as utilization of the Valsalva maneuver.

The criteria are as follows: (1) Hypermotility of the stomach. (2) The characteristic deformity of the duodenal bulb. (3) The ability of the examiner to trace the elongated folds from the stomach through the pyloric canal into the deformity in the base of the duodenal bulb and (4) The absence of a "quick" duodenal bulb.

THERAPY

Therapy in cases of prolapse of the gastric mucosa into the duodenum is directed along physiological lines to try and reduce the relative obstruction in the pyloric canal by the use of antispasmodics and a soft or liquid diet; and, contrary to earlier opinions, antacids. Not all cases profit from the use of antacids but many of them do, and these cases may well have at least minimal ulceration of the prolapsing folds or may even have a duodenal ulcer which is masked by the prolapsing folds. Another objective in therapy of prolapsed gastric mucosa is the treatment of associated conditions such as gastritis, etc., which tend to aggravate and potentiate the prolapse. Psychotherapy and mild sedation are also of value in a fair number of these patients. Most prolapse cases respond adequately to conservative, medical treatment although recurrence of symptoms is not usual, especially when the patient hazards dietary indiscretion or undergoes unusual psychic trauma.

A few patients with prolapsed gastric mucosa require surgical intervention; and the indications are largely the same as they are for duodenal ulcer, namely obstruction, recurring bleeding and intractable pain. The obstruction of prolapse is rarely complete, and when surgery is indicated it is usually for frequent vomiting. Although the author has found no case reports of patients suffering fatal hemorrhage from a prolapse, it is not at all unusual for these patients to bleed profusely; and recurring severe hemorrhages may well indicate surgical correction. Occasional patients may merit surgery for their prolapse on the basis of intractable pain; but such patients must be evaluated carefully preoperatively, and if there is evidence of emotional instability the symptomatic results of the surgery may be disappointing.

SUMMARY

An understanding of the etiology, pathogenesis, clinical implications, diagnostic factors and therapeutic aspects of prolapsed gastric mucosa is offered in an attempt to clarify the confusion and controversy occasioned by the conflicting literature on the subject. "Physiological" and functional, as well as anatomical, considerations are made.

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MEMBRANOUS STAPHYLOCOCCAL ENTERITIS AFTER ANTIBIOTIC THERAPY; REPORT OF TWO CASES*

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SINCE THE advent of antibiotic and chemotherapeutic agents, unusual or bizarre bacterial infections have been observed with increasing frequency. This has been attributed to the development of resistant bacterial strains, or to disturbances in bacterial relationships. Two such unusual cases have recently come to our attention, in which Staphylococcus aureus apparently produced a fatal pseudodiphtheritic membranous enteritis and septicemia postoperatively in patients treated with several antibiotics.

CASE SUMMARIES

Case 1. H. M. (136332), a 43-year-old white salesman, developed ulcerative colitis at the age of 31 years. During the ensuing twelve years he had an ileostomy, a subtotal colectomy, and an ileo-sigmoidostomy. In January, 1952, he was hospitalized for fatigue, fever and dehydration. Admission diagnoses were acute upper respiratory infection and acute ulcerative sigmoid colitis and proctitis. No nose and throat culture was taken. He remained febrile with temperature rising to 104°F on the fourth and fifth hospital days. From the first through the fourth day he received chloramphenicol every six hours for a total dose of 6.25 gm. On the fourth day he was given 400,000 units of penicillin intramuscularly. On the fifth day he developed a generalized erythematous rash. Because of the rash all previous medication was discontinued and gantrisin ® (3,4-dimethyl, 5-sulfanilamido-isoxazole) was started orally, 1.0 gm. every 6 hours and continued throughout the following 11 days. Temperature gradually returned to normal by the ninth day. During the febrile episode chest X-rays showed no evidence of disease; no cultures were taken.

On the twelfth hospital day the ileosigmoidostomy was resected, and the rectum removed from below. Ileostomy was left intact. Postoperative course was marked by fever and frequent, copious, watery discharges from the ileostomy. Sudden, profound shock developed on the fifth with death on the sixth post-operative day. Antibiotics following surgery included a continuation of gantrisin ®, and parenteral streptomycin every six hours from the first through the third post-operative day, for a total of 5.5 gm. On the fifth post-operative day 0.5 gm. of terramycin was given by slow intravenous infusion.

Autopsy showed all surgical closures intact and no evidence of peritonitis. There was atelectasis of the right lower lobe of lung. The jejunum and ileum were lined by a continuous, yellow-tan, fibrinous, "pseudodiphtheritic" cast which was easily lifted intact from the bowel lumen. Culture of this membrane grew hemolytic Staphylococcus aureus and Pseudomonas aeruginosa. Culture of the heart's blood grew hemolytic Staphylococcus aureus. Microscopic examination of intestine showed necrosis of mucosa. The overlying cast was composed of fibrin with numerous polymorphonuclear leukocytes. Gram stain of this membrane revealed many clusters of gram positive cocci buried in fibrin (Fig. 1). No antibiotic sensitivity tests or demonstrations of toxic products were made.

Case 2. V. S. (136500), a 62-year-old, white married housewife, had been admitted in February, 1951, for right upper quadrant pain associated with nausea, bloating, and eructation, at one time with clay-colored stools. Ten years previously she had had a cholecystectomy and appendectomy. In February, 1952, she was hospitalized because of two months of vomiting episodes occurring every 2-3 days and lasting 8-10 hours. She had been receiving aureomycin, dose unknown.

On physical examination no jaundice was found, the liver was 2 cm. below the right costal margin, the spleen not palpable. Pyelograms and barium enema

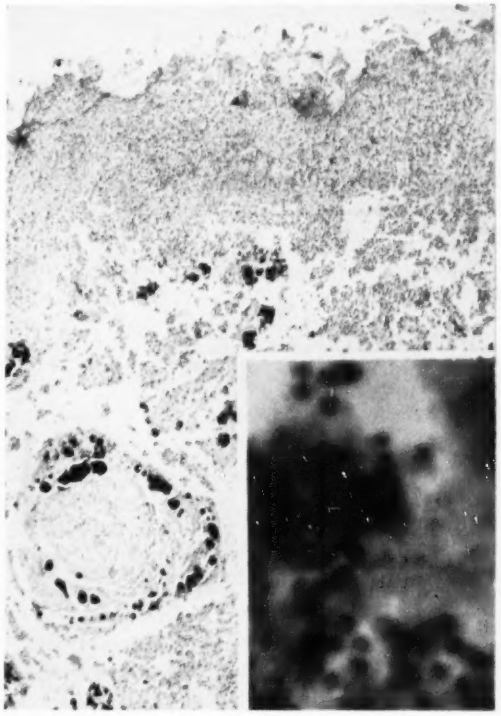

Fig. 1. Case 1.: Portion of cast from small intestine. Gram stain demonstrates the staphylococcal colonies as dark clumps, X50. Insert shows detail of Staphylococci, X3000.

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were interpreted as normal. She was given a convalescent ulcer program with Banthine ®, 50 mg. 4 times daily. She improved and was discharged 5 days after admission with diagnoses of recurrent chronic pancreatitis and biliary dyskinesia.

Two days later she was readmitted with the same complaints of severe vomiting and pain in the right upper abdominal quadrant. There was generalized tenderness over the upper abdomen on deep palpation. An upper gastro-intestinal X-ray examination was reported as normal. Because of the persistence of symptoms, four days later at laparotomy a gastro-enterostomy was performed with exploration of the common bile duct. Her three day postoperative course was one of progressive circulatory insufficiency with fever ranging between 101° and 105°F. She was given transfusions and intensive chemotherapy. Chemotherapy post-operatively included a total of 2.75 gm. of terramycin intravenously, penicillin 250,000 units every six hours, streptomycin 0.5 gm. every six hours, and aureomycin 0.25 gm. subcutaneously. She expired three days after the operation.

Autopsy revealed fibrinous adhesions with adjacent focal peritonitis in the duodenal region, and about 100 ml. of clear, straw-colored, peritoneal fluid. The most significant finding was a soft, wrinkled, tan-pink, fibrinous cast beginning at a point about 10 cm. below the gastro-jejunostomy and extending distally throughout the entire small intestine. The membrane could easily be peeled from the mucosa. There was no leakage at the gastro-jejunostomy suture line. The inverted antral stump was also sealed. The duodenal area was edematous, indurated, and firmly adherent to the underlying tissue. A 2 cm. penetrating peptic ulcer was present on the posterior duodenal wall about 1 cm. above the ampulla of Vater. The ampulla and common bile duct were patent, with a T-tube in place in the latter.

Microscopically, the small bowel showed severe acute and chronic inflammation with very little remaining epithelium. Sloughed mucosa was present in the lumen. Attached to the inner intestinal surface there was a thick membrane composed of fibrin and leukocytes. A gram stain of this inflammatory exudate revealed many colonies of staphylococci (Fig. 2). The stomach and colon were not abnormal. The liver grossly had yellow spots distributed uniformly throughout. On microscopic examination fine fatty infiltration and hepatic cellular atrophy were seen. Portal areas appeared normal. The peritoneal surface of the pancreas was covered by acute fibrinous peritonitis.

Bacteriologic culture of the abdominal wound taken several hours before death revealed Staphylococcus aureus and non-hemolytic streptococci. Cultures of the heart blood at autopsy were reported to show Staphylococcus aureus and Streptococcus anhemolyticus. The bowel cast was reported to contain Streptococcus anhemolyticus and B. proteus. Bacterial sensitivities to antibiotics and toxin production were not investigated.

In neither of these two autopsied cases were extensive bacteriologic studies made. In both a thick fibrinous intestinal membrane was formed, within which staphylococcal colonies grew. This is evidence of positive coagulase activity in vivo, one ordinary criterion of staphylococcal pathogenicity. Changes found in the other viscera were those associated with fatal toxemias. Elaboration of staphylococcal enterotoxin was not proved, but may reasonably be stipulated.

Very few bacteriologically proved fatal cases of this type are recorded. Kramer (1) reported the case of a baby treated for diarrhea with oral streptomycin, who went into shock and died after 3 days. At autopsy a pure culture of Staphylococcus aureus was obtained from the terminal ileum. This organism had not been present in serial stool cultures during life. Zischka (2) described a case in which a child died after two days of sulfaguanidine treatment for vomiting and diarrhea. Autopsy culture from the small intestine showed Staphylococcus pyogenes aureus overgrowing E. coli and Enterococcus. The presence of staphylococcal enterotoxin was demonstrated by the Dolman kitten test, which is considered unreliable. Dixon and Weisman (3) of Mayo Clinic discussed fatalities following bowel surgery, in which autopsy revealed pseudomembranous enteritis. Cultures of stools and bowel mucosa were reported as "negative for the usual bacillary or parasitic agents which produce primary enteritis," and "no intestinal pathogens." These authors noted an increased number of such cases coincident with the institution of sulfonamide therapy in preparation for intestinal surgery.

Staphylococci in the upper respiratory tract can readily be swallowed, washed or carried with Levine tubes into the gastrointestinal tract. Chapman (4) with an improved method of culturing Staphylococcus aureus claimed to isolate this organism in about one-third of fecal samples from "chronic invalids." Staphy-

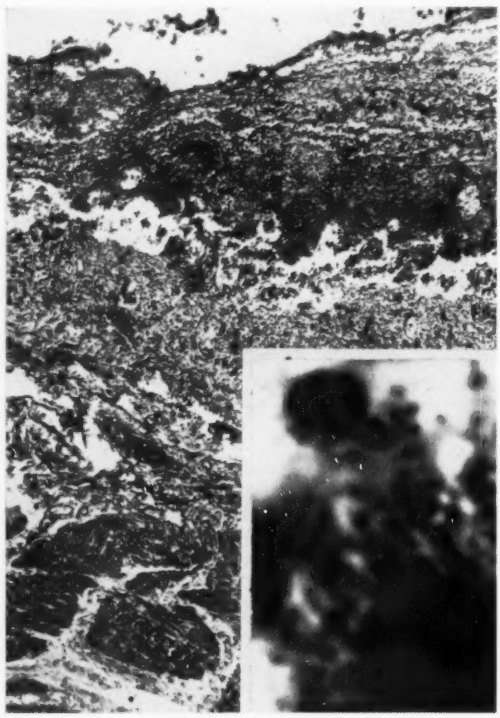

Fig. 2. Case 2: Intestine with overlying membranous cast, X50. Insert is an enlargement of Staphylococci present, Gram stain, X3000.

lococcus enterocolitis may be infrequent partly because of the antagonistic action of E. coli upon its growth. Waksman (5) and Gundel and Himstedt (6) showed that intestinal staphylococci are ordinarily suppressed or destroyed by the E. coli. If, however, antibiotics have attenuated or destroyed the E. coli, staphylococci may grow more readily in intestine, where they can produce toxins and enterocolitis under favorable circumstances.

Ingestion of preformed enterotoxin in cream puffs and other foods causes a different type of staphylococcal disease, quite distinct in its pathogenesis.

Antibiotics vary in their effectiveness against different bacteria. Dearing and Heilman (7) have found aureomycin most effective in sterilizing the bowel. Schnitzer et al (8) have found that gantrisin ®, (3,4-dimethyl, 5-sulfanilamido-isoxazole or NU 445) has moderate activity in vitro against gram positive organisms but possesses a pronounced bacteriostatic effect against gram negative bacteria.

The present tendency is to treat infections with one or more antibiotics which may temporarily rid systems, organs or tracts of the normal bacterial flora. It is important to realize that antibiotics can radically alter bacterial relationships. Pathogenic organisms ordinarily barred locally by the antagonistic action of the bacteria usually present may grow in a field from which the normal bacterial flora has been eliminated. Such a phenomenon evidently occurs in some cases of staphylococcal enteritis. In this particular situation nose and throat cultures prior to and during antibiotic therapy might be useful as an indication of what bacteria were predominant and would serve to aid in the choice of antibiotic agents.

Summary

Two fatal cases are reported of membranous enteritis associated with Staphylococcus aureus septicemia and the presence of staphylococci in the fibrinous enteric casts. Attention is directed to this as an apparent sequel of antibiotic therapy, consequent upon radical alterations of the normal intestinal bacterial relationships.

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PRELIMINARY REPORT ON THE EFFECT OF SMOKING ON THE ASCORBIC ACID CONTENT OF WHOLE BLOOD

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THE CAUSE and control of oral lesions are not well understood. Gingivitis brings many students on our campus to the Student Health Office. No doubt, our campus is no exception. Because the majority of these students are heavy smokers it seems not unlikely that this may be one causative factor. In 1949 Pindborg (1) having observed 5,690 Danish Royal Marines reported a relationship between the use of tobacco, ulcerative membranous gingivitis and the deposition of calculus. Following this Frandsen, et al (2) noted a greater formation of calculi in pipe smokers than in those smoking cigarettes. They attributed the higher number of calculi in pipe smokers to the greater salivation when the tobacco is used in this form. Schnedorf and Ivy (3) had previously observed increased salivation during smoking.

Another approach to the study of gingivitis has been in connection with nutrition studies. The nutrients which when lacking in a diet have been reported as resulting in gingivitis are vitamin A and ascorbic acid (4). Of these ascorbic acid is the nutrient most frequently associated with this condition and is most often prescribed along with other treatment. Youmans and many others (5) have stressed the relationship between gingivitis and a lack of dietary ascorbic acid and Kruse (6) has suggested that the presence of gingivitis can be used as a simple, convenient, objective means for detecting an ascorbic acid deficiency. It seems very possible that smoking may play more than a purely mechanical part in its relationship to gingivitis. It is well known that nicotine is absorbed into the blood stream and is toxic. In the British Medical Journal, Scott (7) gives an excellent review of the subject. It is also believed that one of the functions of ascorbic acid is to serve as a detoxifier (8). It is entirely conceivable that smoking may lower the blood level of ascorbic acid and hence bring about conditions which may predispose the individual to develop symptoms of an ascorbic acid deficiency. An investigation was, therefore, set in motion.

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Experiments in Vivo

Experiments were planned in vivo and in vitro. Five subjects were chosen, four women and one man. Three

of the subjects were smokers and will be spoken of as the experimental group. The two who did not smoke comprised the control group. This investigation was divided into three periods. Period A was a period of three or four days when the subjects reported to the laboratory in the morning for a blood test having had only a breakfast of cereal and coffee. Other than at breakfast the subjects were permitted to follow their own individual patterns of eating and smoking. Of the women, Subject II smoked about a pack of cigarettes a day and did not consciously inhale. The other, Subject I, smoked about 1/6 of a pack of cigarettes a day. The man, Subject III, was accustomed to smoking 1½ to 2 packs per day and inhaled as he smoked.

During the next two periods the group came to the laboratory for their meals or were given their food to eat at home. The food was weighed and the diet was adequate according to the National Research Council recommendations (9). The adequacy of the diet was calculated using the tables of Bowers and Church (10). The food was chosen so that the 75mg. of crystalline ascorbic acid given, was the only ascorbic acid received each day except that contained in 720 gm. of pasteurized milk which was daily consumed by each member of the group. The menu consisted of the same foods each day and the ascorbic acid was divided into two portions. Fifty milligrams were taken at noon and 25 milligrams at night with dinner. It was hoped by this procedure to bring about not only a controlled source of ascorbic acid but to make the intestinal conditions for absorption consistent. Blood was drawn as in period A following a light breakfast. These two periods were each four days and differed only in that during period B no smoking was permitted. During period C smoking was resumed as in period A except that the light smoker, Subject I, increased her consumption to a half pack of cigarettes per day. The controls, of course, did not smoke. The three periods followed each other without an intervening period for physiological adjustment. No food was permitted other than that given the subject and the use of aspirin and other drugs was omitted. The activity of all subjects was similar since they were all engaged in academic work. However, records were kept of hours of sleep, strenuous exercise, elimination, appetite and general well being. The condition of the smokers remained excellent during the experiment. One control developed a cold during period C. Her last blood test was, therefore, omitted. The other control found the diet too high in fat and developed diarrhea which was corrected when carbohydrate was substituted for some of the fat. During the period of diarrhea her blood ascorbic acid dropped and, therefore, those days were omitted from her average ascorbic acid blood levels for periods B and C.

The blood was drawn from the finger usually flowing freely with only slight pressure being needed.

The analysis was done in either duplicate or triplicate by the method of Roe and Kuether (11) adapted to the micro-attachment of the Evelyn Photoelectric Colorimeter.

EXPERIMENTS IN VITRO

To whole fresh human blood was added enough crystalline ascorbic acid to make the samples approximately equal in their ascorbic acid content. This blood was divided into two parts. One sample of blood was immediately analyzed for its ascorbic acid level. To the second sample of blood was added an amount of nicotine roughly calculated to equal the amount of nicotine which might be absorbed by a person who was a heavy smoker and who inhaled. After mixing, the ascorbic acid content of this sample was determined.

RESULTS AND DISCUSSION

As it will be seen from the averages of the Control Group in Table I there was a decrease in the average of the ascorbic acid level of the whole blood in periods B and C even though this group did not smoke. However, it will be remembered that it was in this group that the physical condition of the subjects was not all that could be desired. In Control I we found that the blood level dropped a little lower than the average level for period C on the last two days of period B and that a heavy cold developed on the third day of period C. Control II developed diarrhea the third day of period B with a resultant drop in ascorbic acid blood levels and it was not controlled until the third day of period C. Hence the average for this period really consists of a single determination, the fourth day of the period when the ascorbic acid blood level had risen somewhat.

Although all the subjects in the experimental group showed a drop in their average ascorbic acid blood levels, there seems to be no consistency in the results. It was regretted at the start of this study that subjects more nearly alike in their smoking habits could not have been obtained. However, the results of the experiment did prove interesting. It will be noticed that 75mg. of ascorbic acid did not greatly raise the average blood level of ascorbic acid in the case of subjects II and III in period B. It will be remembered that these two subjects were the two who consumed the greatest number of cigarettes. Particularly was subject III addicted to smoking and it was this subject who consciously inhaled. Wolff, et al (12) reported that nicotine can be found in the blood ten hours after the last cigarette has been smoked. Had the periods not immediately followed each other the averages might have been different. Although the consumption of ascorbic acid was not checked in period A, it is of some interest to note that subject I, the light smoker, maintained her blood level in period B, that subject II showed an appreciable rise on the first day of period B while subject III showed no rise on the first day of this period. Subject III also was the one who suffered from dizziness on the resumption of smoking in period C and it will be observed that it is this subject that showed the most marked drop in ascorbic acid level of the blood, 66%, when smoking was resumed.

TABLE I

Showing the Average Level of Ascorbic Acid in Whole Blood During Periods of Smoking and Non-Smoking

Control Group		Period A Diet Unrestricted	Period B Diet Restricted	Period C Diet Restricted	% Decrease
Subject I	Female	1.24 mg %	1.02 mg %	0.95 mg %	8.8
Subject II	Female	0.92 mg %	0.88 mg %	0.81 mg %	7.9
Experimental Group		smoking	no smoking	smoking	
Subject I	Female	1.03 mg %	1.02 mg %	0.85 mg %	16.6
Subject II	Female	0.62 mg %	0.70 mg %	0.62 mg %	11.4
Subject III	Male	0.44 mg %	0.51 mg %	0.17 mg %	66.0

EXPERIMENTS IN VITRO

When nicotine of a strength thought possible for the blood of a heavy smoker to attain is put into whole blood of known ascorbic acid content, a decrease in ascorbic acid from about 24% to 31% resulted. The amount lost seems to depend upon the time which elapsed before the analyses were made. This is shown in Table II.

TABLE II

Effect of Nicotine on the Ascorbic Acid Level of Whole Drawn Blood

Sample	Whole Blood, % Ascorbic Acid in,	Whole Blood and Nicotine Time of Contact	mg% of Ascorbic Acid Recovered	% Loss of Ascorbic Acid
I	1.20	10 min.	0.82	31.6
II	0.90	5 min.	0.68	24.4
III	1.07	5 min.	0.81	24.4

In searching the literature no comparable report of work testing the effect of smoking of nicotine on the ascorbic acid level of blood has been found. McCormick (13) does state that smoking one cigarette neutralizes 25mg of ascorbic acid in the body but no details were given of the experiment. Reif (14) reported a series of experiments in which nicotine was added to a water solution of ascorbic acid where significant destruction of ascorbic acid occurred. Strauss and Scheer (15) in working with human subjects found a decrease in the urinary excretion of ascorbic acid when the subjects were smoking. In the light of this supporting work it seems reasonable to conclude that under the conditions of this experiment, smoking cigarettes does influence the blood level of ascorbic acid of the smoker. The degree to which the blood level will be lowered will depend upon the amount and the manner of smoking and possibly, as with the lighter smoker, the amount of nicotine to which the body may be accustomed.

The way in which ascorbic acid is removed from the blood by nicotine is not known. Strauss and Scheer suggest that the decrease is related to the endocrine mechanism especially the thyroid and the adrenals and to the vegetative nervous system. They believe that the nicotine increases endocrine activity enhancing the level of the general oxidative activity in the body and, therefore, the need for ascorbic acid. Ershoff (16) considers that the ascorbic acid combines with the toxic substance and is withdrawn from the blood in its active form. He postulates that the product formed by this union is excreted in the urine. It is, of course, possible that both of these mechanisms may be at work. Clinicians have taken advantage of this detoxifying effect of ascorbic acid and are giving increased amounts of ascorbic acid when toxic drugs are prescribed as described by Schaffer and co-workers (17). Perhaps nicotine (smoking) should be added to the list of toxic substances and that the amount of ascorbic acid should be increased in the diet of those who are accustomed to habitual heavy smoking.

SUMMARY

The effect of smoking on the ascorbic acid level of the blood was investigated. Five subjects were chosen, three of whom smoked (the experimental group) and two who did not smoke (the control group). Three periods were planned of four days each. The groups were placed in the second and third periods on a controlled diet and the blood level of ascorbic acid was determined during a period of smoking and during a period when no smoking was permitted. The blood level of ascorbic acid appears to be lowered by smoking.

Nicotine was added to a sample of whole human blood of known ascorbic acid content. Nicotine added under the conditions of this experiment decreased the ascorbic acid of whole blood about 24 to 31 per cent.

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PRACTICAL DIAGNOSIS OF PANCREATIC DISEASE

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Introduction

THE PANCREAS is an elusive organ, hidden to the eye of the clinician and of the x-ray man, confounding sometimes even the surgeon. Diagnosis depends upon the laboratory. The diagnostic aids here martialled are ones that can be done easily in any small laboratory or hospital without recourse to complex apparatus or to unfamiliar and discouraging techniques. Tests of pancreatic function usually emphasized, for the most part vague, ambiguous, and worthless, are not included. The philosophy is that of the Gastroenterology Service at the present time at Madigan Army Hospital: after 90% of the pancreas has been removed by operation or by disease, completely normal function may yet remain (33) so that diagnosis is fore-doomed, and the simpler the study, the better. It is hoped that physicians will be moved to familiar use of these fundamentals which point the way to diagnosis.

No review of pancreatic tests is complete without an expression of indebtedness to Dr. J. H. Pratt of Boston, who pioneered the study of complex pancreatic physiology in this country, and who yet has always stressed diagnostic methods.

Anatomical and Physiological Considerations in Pancreatic Diagnosis

Studies of pancreatic anatomy demonstrate that in 40-60% of people the common bile duct and the pancreatic duct are united in a common ampulla (27). The argument still rages how much reflux of bile through this common channel contributes to the beginnings of chronic pancreatitis, but we are concerned here only with the fact that there may be an entrance for the accessary pancreatic duct separate from that of the ampulla of Vater. This will explain to us discrepancies in duodenal drainage results and in stool analysis.

Calcification in the body of the pancreas by x-ray, a large duodenal loop, disordered motor function of the bowel, or, in early life, involvement of the lungs with fibrocystic disease, are of some diagnostic value; but too often there is no anatomical evidence of disease. It is only by variations in the function of the pancreas itself that we can uncover the organ we seek. These functions are to regulate:

(1) Carbohydrate metabolism, by insulin production.

(2) Digestion, by digestive ferments.

(3) The reaction of the intestines, by secretion of bicarbonate.

The pancreas is a gland built like a bunch of grapes, with alveoli lined by cells that produce the enzymes. The secretion is collected from these alveoli by branches of ducts which flow into the main pancreatic duct and thence through the ampulla of Vater into the duodenum. It is suggested by Grossman and Ivy (14) that the cells lining the ducts supply the bicarbonate and water to the pancreatic fluid. Whether the pancreas secretes fluid rich in the digestive enzymes or in bicarbonate is determined by the type of digestive stimulus (33). During the interdigestive phase, enzyme secretion is also somewhat influenced by diet: animals fed on carbohydrate have high pancreatic amylase secretion.

There are three phases of human pancreatic secretion, but it is notable that there is no gastric phase of pancreatic secretion:

(1) A continuous secretion, unrelated to digestion, is demonstrable at duodenal drainage.

(2) A cephalic phase, corresponding to vagal "appetite" juice and to the cephalic phase of gastric secretion, consists mainly of increased enzymes.

(3) The intestinal phase of pancreatic secretion is the one usually evaluated by functional tests, and involves the hormones secretin (to stimulate the duct cells to produce water and bicarbonate) and pancreozymin (to stimulate enzyme out-flow).

Acid is the most potent stimulus of alkaline secretion, probably directly owing to its evoking of secretin. The resulting secretion, high in bicarbonate, may be purposefully related to a need to neutralize hydrochloric acid of the stomach (33). Fats, stimulating sapocrinin, a hormone believed analogous to pancreozymin, give rise to pancreatic fluids high in enzymes. Carbohydrate probably dictates the secretion of enzymes through the local action of a high blood sugar on the gland; nevertheless, a low blood sugar is equally stimulating by an effect on the vagal centers. Many drugs excite pancreatic secretion when placed in the intestine, as ether and magnesium sulphate; of systemic drugs particularly important are the parasympatheticomimetic agents which stimulate small quantities of juice high in enzymes. All these are utilized in pancreatic assay.

The simplest laboratory tests of pancreatic function, therefore, will involve:

1. Examination of the fecal residue, the components of which depend upon pancreatic function.

2. The measurement of pancreatic enzyme levels.

   (a) In the duodenum.

   (b) In the blood.

Examination of the Stool

By examining the residue, we can tell how well the pancreas has functioned. Carbohydrate, fat, and protein all pass through the gastrointestinal tract and may be found in the stool. Naturally, this depends in part upon attending intestinal motility and intestinal absorption, but if the following tests are abnormal, one must consider the pancreas strongly indicted. A standard

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SCHMIDT TEST DIET

BREAKFAST:
1 pint of milk
50 grams of zwieback or dry toast

1000:
1 pint of cereal gruel made up of 40 grams of rolled oats
20 grams of butter
200 grams milk
300 grams water
1 egg
salt to taste

LUNCH
125 grams chopped meat (beef weighed raw), broiled with 20 grams butter
250 grams potato

1600:
Same as breakfast

SUPPER:
Same as 1000

CHO	PRO	FAT
226.26 Grams	107.94 Grams	156.70 Grams

TOTAL CALORIES
2744

Fig. 1. The Schmidt Test Diet for pancreatic assay.

diet is usually prescribed, but may be omitted in clinical diagnosis. A modification of the Schmidt diet used at Madigan Army Hospital is found in Figure 1.

Weight of the Stool

The simplest test is to weigh the stool! Normally, the moist stool weighs 100 to 200 grams, and averages 115 grams on a Schmidt diet (32). When the daily stool weighs over 300 grams, obstruction of the pancreatic ducts must be suspected (25). In 5 representative cases of carcinoma of the pancreas, Pratt found values ranging from 340 to 460 grams. If there is associated blocking of the common bile duct, even larger weights may be recorded; whereas common duct obstruction without pancreatic disease leads to no more than 220 grams of stool. The increased bulk in chronic pancreatitis may reach 300 and 400 grams.

Fat in Stool

1. *Mechanism of absorption* (12):

a. The fats are split to *fatty acids* by pancreatic lipase and are then absorbed, through phosphorylation, as phosphatides, passing into the portal stream and the liver.

b. Emulsified by bile, very small particles of fat are absorbed directly as *neutral fat*, passing into the lymphatics and thence into the thoracic duct.

Fat, however, is always present in the feces in the amount of about 12 grams a day, which is equal to 5-10% of the amount ingested (15, 23). Recently, excretion of fat by the intestine has been demonstrated, since the stool even in the fasting patient may contain up to 36% fat (23, 29).

2. *Fat and Fatty Acid Partition*

It is usually believed that in the absence of pancreatic enzymes, the stools show deficient fat splitting. Any stool with neutral fat exceeding 11% of the total dry matter (or 55% of the total fat) is abnormal (11). When the patient is on the Schmidt diet, 30-50% of free neutral fat in the stool denotes pancreatic disease.

Contrarily, one demonstrates poor gastrointestinal absorption by excessive split fat in the stool; although the pancreas has done its work well, the split material has just not been absorbed. Any stool with total split fat exceeding 16% of the dry weight (or 75% of the total fat) has deficient fat absorption (11). This is of some clinical significance since only stools full of *neutral* fat have solid masses of buttery material present: only the stools of pancreatic steatorrhea have visible "butter;" in celiac disease and sprue (where the major disability is in the fatty acid fraction), the stools are foul, frothy, and foamy, but they are not "buttery."

There is little value, however, in trying to differentiate split fat and fatty acids in diagnosis, little value, that is, in view of the difficulty of the tests. For we have already noted that re-excretion of fat by the intestine occurs; the fat may be in either form and therefore has little to do with the state of pancreatic enzymes. Further, even after ligation of the pancreatic ducts, only one-third of the fat excreted is neutral fat; the rest is soaps and fatty acids, a fact which makes laborious assessment of the fat partition unwise.

3. *Anderson Slide Test*

For clinical estimation of the stool fat, there is a test simple and easy, but often ignored, recommended by Anderson (1). A small amount of stool, smeared with a few drops of Sudan III and pressed out on a cover glass, is examined under the microscope. The fat droplets are then seen as orange globules, while fatty acid appears as orange-red crystals. In a low power field, one or two of these are perfectly normal; quite often none may be seen.

However, if the amount of fat is graded from 1-4 (1 equals 1-2 drops per low power field and 4 equals half the field covered by fat), Anderson has shown that Grade I means that the total fat is normal, does not exceed 30% of the dry weight. If there are enough droplets to cover half of a low power field, there is a definite excess of neutral fat and pancreatic disease is to be expected. This simple test can be done in less than five minutes!

One series of patients following resection of the head of the pancreas lost about 50% of ingested fat in the stool, as compared with the normal 5-10%; this was decreased considerably by the administration of pancreatin (35). Unfortunately for one's diagnostic acumen such gross differences are not always present. In patients with chronic relapsing pancreatitis, only when there is definite evidence of pancreatic disease (diabetes, calcification, or buttery stools) is the diagnosis confirmed by stool fats; when at least one of these stigmas is not present, the fecal fat may be normal (9). The Anderson slide test is so easy, however, that it should not be neglected.

Protein in the Stool

Protein digestion provides an approach to the diagnosis of pancreatic disease from another aspect. Trypsin and other pancreatic enzymes are essential for the complete digestion of muscle fibers (23).

1. *Microscopic Examination*

Normally under the microscope the muscle fibers of meat are pretty much digested when found in the stool (26); their long and transverse striations are dissolved and the nuclei have been destroyed. However, if trypsin is absent from the stool, the characteristic appearance of muscle fibers (much like they appear in an H & E stain) may be expected. The presence of nuclei of muscle cells is further evidence of lack of pancreatic enzymes since only pancreatic enzymes can digest nucleoprotein. Pratt urges that the fatty stool of sprue and obstructive jaundice can be differentiated from that of pancreatic disease by this simple observation: in sprue and in obstructive jaundice the muscle fibers are well digested, in pancreatic disease they are not.

2. *Shwachman "X-ray" Test*

Shwachman (30) has used to advantage the fact that the normal child passes active trypsin both in the normal stool and in diarrhea and has devised a test to exclude pancreatic insufficiency in celiac disease. He dilutes the stool with saline 1 to 5 and 1 to 10 and drops it on exposed x-ray film which is then allowed to stand at room temperature for two hours. The presence of clearing on the film displays digestion of the protein film emulsion. If trypsin is present, the x-ray film clears and the integrity of the pancreas is proven. If there is no trypsin in the stool, the x-ray film does not clear and further studies are necessary to determine the degree of pancreatic insufficiency.

Indeed, if there is no laboratory available, a duodenal drainage may be carried out, and a good estimate of the amount of trypsin present in the pancreatic fluid may be made from placing the duodenal fluid on the x-ray film and reading the degree of clearing. (Figure 2.)

In the adult, however, the test is applied only tentatively: the normal adult stool contains trypsin only when the patient has diarrhea. Therefore, the

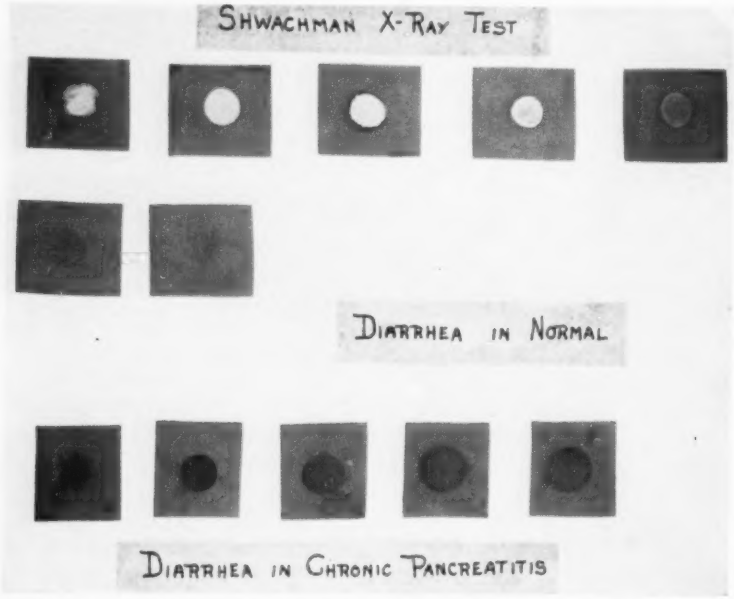

Fig. 2: In this example, clearing of the x-ray film appears as a light area in the center of the squares of x-ray film. The upper series shows serial dilutions of a normal stool following catharsis with demonstration of the presence of trypsin in the stool. The lower series shows no clearing of the x-ray film and demonstrates the absence of trypsin in the stool.

patient is given a strong laxative and, if there is no digestion of the x-ray film by the stool following catharsis, one considers further the possibility of pancreatic disease. In a series of 70 adults given laxatives, trypsin was determined in the stool (by another method), and of the six stools without trypsin, all had proven pancreatic disease (30).

Nitrogen in Stool

The amount of nitrogen in the stool may also be determined, but this is not a simple procedure and is mentioned only because of its absolute value. Normally, on a regulated Schmidt diet, 1-2 grams of nitrogen are excreted daily (25, 11). If the total is 3 grams or over, pancreatic disease is a definite possibility (25). Even in diarrhea due to other causes, the fecal nitrogen rarely rises above 2 grams, and the general consensus is that sprue and other pancreatic disorders may lead to a rise in fecal nitrogen which never goes above 3 grams.

In ten patients without the three primary criteria of pancreatic disease, the fecal nitrogen was between 1 and 2.5 grams, but in cases with the three criteria, the fecal nitrogen was always 3 grams (9). What part the excretion of nitrogen by the colonic mucosa plays is, of course, uncertain.

EXAMINATION OF THE DUODENAL CONTENTS

Secretin Test

Hydrochloric acid has been known to play an important role in stimulating pancreatic secretion ever since Bayless and Starling demonstrated in 1902 that extracts of the mucous membrane of the jejunum injected intravenously stimulated pancreatic secretion. Secretin, which is the responsible agent isolated from the duodenum and the jejunum, has been crystallized (3), but mystery still surrounds its function and its method of action. We know only that it calls the hydrochloric acid of the stomach cells into play in normal digestive secretion.

The secretin test, demonstrating the intestinal phase of pancreatic secretion, is simple and standardized. It is too bad that results are not as uniform. A standard dose of secretin in the normal gives a maximal secretion of fluid with a constant concentration of bicarbonate (33); but the enzymes are not specifically stimulated and are less in amount than that produced by fat in the duodenum or by "appetite" juice (17). By the variations in the pancreatic response is displayed the functional capacity of the gland. However, the total enzyme output, its concentration, and the amount of bicarbonate does vary with the type of stimulus. Pancreozymin, which stimulates a profuse specific flow of enzymes and rather less of fluid and bicarbonate (3), will someday be of more value in secretion studies.

When secretin is given, if pancreatic fluid is withdrawn by means of a duodenal tube, there is found an immediate secretion of pancreatic juice and of bile which reaches a maximum during the first ten minutes following injection. Enzymes, not specifically stimulated, are diluted and drop to a low level in the duodenal aspirate during the second ten minutes, thereafter running along at a fairly low level of output throughout the test. Lagerlof (17) describes two types of isolated abnormal pancreatic response:

1. Type I—a reduction in the amount of amylase occurs in moderately severe, or in mildly acute, pancreatic disease and is probably the result of acute edema.

2. Type II—a reduction in the volume, and more particularly in the bicarbonate, occurs when there is irreversible anatomical injury.

The results really depend upon the site and severity of pancreatic duct involvement. We will not here discuss the legion of work on this subject, much of which is contradictory and disconcerting to the clinician, who is only occasionally called upon to evaluate the results. It is helpful, nevertheless, to have a scheme which will enable us to understand these reports. The accompanying diagrams (Figure 3) are not necessarily completely

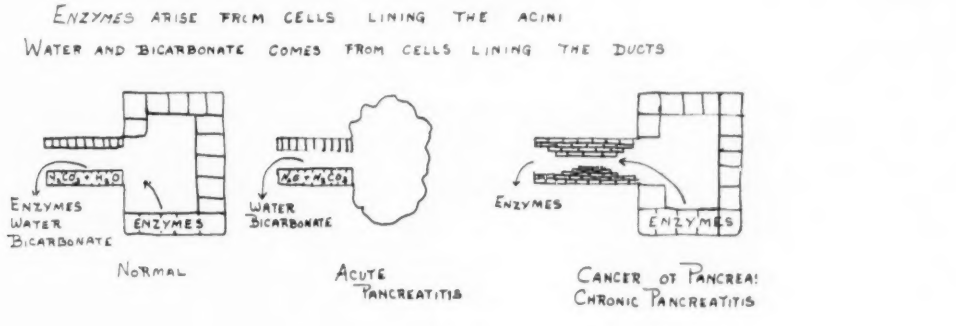

Fig. 3: A theory of duodenal drainage. See text.

accurate, but they have been helpful in trying to understand pancreatic drainage tests; they are presented as a base line from which one can expand. The results are best understood by visualizing the gland drainage system: the pancreatic cells produce enzymes, while the cells lining the drainage ducts most probably give rise to the water and bicarbonate (14). Therefore where there is blockage of the duct, the volume will show a greater decrease than will the concentration of enzymes since the pancreatic acini still function normally, but cannot drain. The fluid that gets by the barrier may well be normal. On the other hand, if the secreting gland itself is atrophied, the depression will be most marked in the enzymes, though, of course, the volume will fall to some extent.

If duodenal drainage is carried out in acute pancreatitis, the enzymes are always disturbed; in severe cases, of course, all components of pancreatic secretion are decreased. Studying 28 cases of chronic pancreatitis, 16 of which had at least one of the three primary criteria of calcification, steatorrhea, or diabetes, Dornberger (9) found abnormal duodenal drainage values in 18 who were without chronic steatorrhea. In 10 of these abnormally low bicarbonate, volume, and enzymes were present, but usually the bicarbonate values and the volume were most helpful. Wainwright's work demonstrating focal metaplasia of the pancreatic duct epithelium in chronic pancreatitis (34), so that the normal cuboidal cells lining the ducts are replaced by squamous cells, makes these results explicable in terms of our diagram. In only 3 of the 28 cases were the enzymes diagnostically low. Others have reported different results; Friedman (13) found rather the opposite, but agreed that the absence of enzymes following a secretin test meant pancreatic disease. Others have used urecholine, olive oil, hydrochloric acid, and the like, with varying opinions.

Lake (18) noted most frequently decrease in the amylase in patients with pancreatic disease. Dreiling (10) studied pancreatic carcinoma and described the greatest change in the volume when there was blockage of the ducts; in acute pancreatitis duodenal drainage revealed the lower values of enzymes; in 7 cases of chronic pancreatitis the bicarbonate fell most of all. Thus, if we keep in mind the basic concept, we can find an explanation for some of these results.

SECRETIN AS A TEST OF GALLBLADDER FUNCTION IN PANCREATIC DISEASE

Normally secretin stimulates secretion of bile by the liver, but this bile never reaches the duodenum because it is concentrated in the gallbladder. Because of this, secretin with duodenal drainage has been used to test gallbladder function (10); normally if the patient is not jaundiced there may be no bile in any sample. If the patient is jaundiced, however, the absence of bile means obstruction in the biliary system. Normally too, the duodenal drainage may have bile in some samples and not in others. If all the samples are heavily colored with bile, it is obvious that the stimulated bile is no longer concentrated and stored up and therefore that there is a non-functioning gallbladder.

PANCREATIC ENZYMES IN THE SERUM

Unfortunately, duodenal aspirations are difficult, time consuming, and uncomfortable. Fortunately, however, the exocrine secretion of the pancreas has its endocrine parallel, and the secretions "back up" from the pancreatic acini into the lymphatics and thence appear in the blood where they may be biopsied. This has been demonstrated recently in the gastric glands—pepsin has its counterpart in uropepsin which passes out in the urine; stimulation with ACTH leads to a parallel rise in both enzymes (31). This "endocrine" aspect of digestive glands is most exciting and is certainly worthwhile developing. If one imagines the pancreas as diagramed in Figure 4, the answer is simple, even though only 40-60% of patients have a common ampulla with the bile duct.

Serum Levels Without Stimulation

It is easy to see that if one blocks off the out-flow duct or ducts, the secretion will back up into the lymphatics and thence into the blood, to make the blood enzyme level rise. This happens in acute pancreatitis. After the pancreatic ducts of a dog are tied, the blood and urine values rise to high levels at once and drop in about a week (26). In a man with acute pancreatitis,

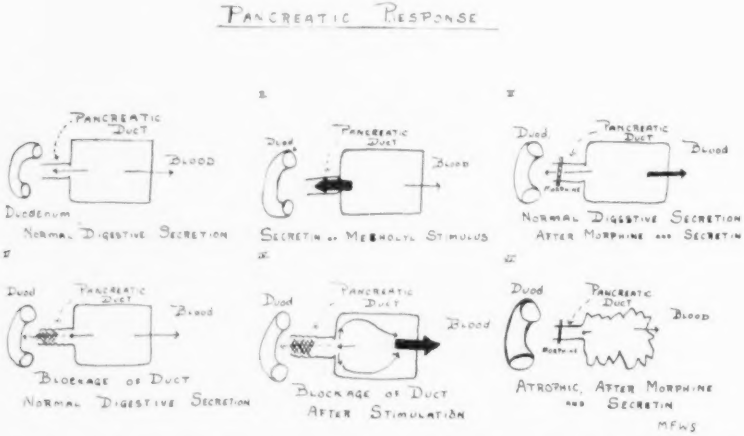

Fig. 4: A scheme of pancreatic enzyme response as reflected by blood levels. See text.

the amylase rises at once in the blood, but drops to normal levels within 24 hours. Concurrently, the urinary amylase reflects this rise, but may remain elevated for as much as a week following acute pancreatitis. This constantly high level must reflect a constant in-flow of enzymes into the blood since normally they are rapidly eliminated (24). Parenthetically also, one should note that aspiration of the peritoneal fluid has yielded high amylases in acute pancreatitis, an elevation which has persisted for at least three days even following the return of the serum levels to normal (16).

The serum lipase is more difficult to do than the amylase and requires 24 hours for its reading, but diagnostically, it is far more satisfactory. It may remain high in acute pancreatitis as long as 4-5 days (26). In 8-22% of the patients with carcinoma of the pancreas, the amylase is found elevated because of blockage of the ducts, while the lipase is high in about 40% (8, 2). Persistent elevation of the serum lipase is a sound indication of pancreatic carcinoma.

Stimulated Serum Levels

The pancreas and its double relation to gut and to lymph demand an easy evaluation of the functional integrity of the pancreas: close the ampulla of Vater with a drug and then stimulate the gland's enzymes so that they back up against the closed ampullary outlet and overflow into the blood. There are two ways this concept has been applied:

1. In order to see whether the duct is blocked by disease, the gland is stimulated by secretin or mecholyl. If there is no blockage, there is no rise in the serum levels. If there is even partial blockage, the greater outflow of enzymes cannot be accommodated and they back up to rise in the serum.

2. In order to see how well the pancreatic cells and acini are functioning, the outlet is blocked with morphine and the gland then stimulated with secretin or mecholyl. If the gland is secreting normally, there is a rise in the serum enzymes. If there is no rise, one suspects that the gland is atrophic.

Popper (24) studied this in dogs, knowing that pilocarpine, and the other parasympatheticomimetic drugs, closes the Sphincter of Oddi, thereby to cause a rise in the serum amylase. He showed that with acetyl-beta-methyl-choline there was a rise in the amylase in normal dogs, but not in dogs with an atrophic pancreas. Others have given secretin to such dogs and have determined the serum lipase. With blockage of the ducts and of the enzyme outflow, the serum lipase rose; by 30-45 days after ligation of the ducts, atrophy of the pancreas had taken place and a rise in the lipase was no longer demonstrable. Lagerlof first gave morphine sulphate to produce spasm in the Sphincter of Oddi, and then, following the morphine with secretin, demonstrated a rise in the serum amylase. Myhre (22) by this same procedure produced in 70% of normals an increase in the serum amylase and in the serum lipase, but in far advanced pancreatic disease, no increase occurred.

Prostigmine leads to no elevation of serum enzyme levels in normals nor in patients with far advanced atrophy of the glands; but if the ducts are obstructed, as by carcinoma, a good serum rise in amylase and lipase has been obtained (7, 21). Morphine, therefore, can be so used to "block" the duct functionally, and makes it possible for the clinician to evaluate pancreatic digestive function by an increase in serum levels. This effectiveness of morphine is owing to the contraction of the sphincter which encircles the papilla of Vater. Indeed, the increase in the common duct pressure, in the pancreas and in the gallbladder following morphine, has suggested that the use of morphine in acute pancreatitis is ill-advised (7, 28). Thus far, the morphine-secretin test and its modifications has proven more helpful in demonstrating the presence of pancreatic abnormalities than in the differential diagnosis of pancreatic disease.

Stimulation of "Latent" Enzymes in the Serum

This work has been carried farther (19) to show that in patients recovering from acute pancreatitis who previously had had high serum amylase and who still have some degree of hyperlipasemia present, secretin leads to a further rise in the serum lipase and amylase. Obviously, this depends upon blockage of the ducts by edema. Of more importance is the fact that in such patients, when the serum values have all returned to normal, secretin still raises the serum amylase and lipase values (19). The lipase rise occurs more frequently and up to a later date, about 10 weeks, following an acute pancreatitis than does the amylase rise. Thus, the clinician who sees a patient after his abdominal pain has disappeared can use this test in restrospective diagnosis. In a few patients with malignant neoplasm in the head of the pancreas, a rise in the serum amylase or lipase has been obtained by these methods (19).

Carbohydrate stimulates pancreatic secretion so that one combines a glucose tolerance with a test of exocrine secretion by giving 100 grams of carbohydrate by mouth; then by serial serum amylases and blood sugars, one determines the patency of the common duct at the same time that he proves the integrity of the isles of Langerhans. Normally, carbohydrate produces a high pancreatic outflow and no rise in the serum amylase. With blockage, the amylase levels rise in the serum.

CARBOHYDRATE METABOLISM IN THE DIAGNOSIS OF PANCREATIC DISEASE

Hyperglycemia was first demonstrated in pancreatic carcinoma in 1893. Thereafter, when Dashiell compiled the cases of fourteen authors, he found the percentage showing hyperglycemia to be 9.4 (8). Of Berk's patients with carcinoma of the pancreas, 24.2% had sugar in the urine (5); in another series 32.4% of patients had glycosuria. Hyperglycemia and glycosuria are profoundly important, therefore, as signposts to pancreatic disease. Dashiell himself had ninety cases of carcinoma of the pancreas in which twenty-one had transitory glycosuria and of these, 60% had hyperglycemia; sixteen had frankly diabetic curves in the presence of only an occasional spilling of sugar in the urine; all had a *normal* fasting blood sugar. Thus, we cannot rely on anything less than a glucose tolerance test to point the way.

Bockus (6) states that four out of every ten patients with carcinoma of the pancreas have hypergly-

cemia, glycosuria or impaired glucose tolerance test. Berk (5) found the glucose tolerance test to be indicative in 77.8% of patients tested. The converse must be considered: 7% of patients with carcinoma of the pancreas have a past history of long standing diabetes. Marble (20) notes that carcinoma of the pancreas is 6 to 16 times as prevalent among diabetics as among normals and is the most common tumor of the diabetic.

CONCLUSION

The hard terrain of pancreatic diagnosis has been traversed. Looking back, we can see certain definite landmarks:

(1) The examination of the stool.

(2) Serial serum enzyme levels.

(3) Stimulated serum enzyme levels.

(4) Blood sugar levels.

All these tests are easily done. Duodenal drainage, which has been discussed, may be helpful, may be confirmatory, but is probably not worth the effort; the presence of blood in the aspirate may localize disease. Papanicalaou studies of the duodenal aspirate are valuable, but unfortunately the necessary technical assistance is not universally available.

The ultimate in pancreatic diagnosis has not been described, nor yet have the most complete pancreatic diagnostic tests necessarily been covered. However, from the vantage point of the practicing medical officer, the simplest and the most practical tests for everyday diagnostic use have been amplified.

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EDITORIAL

HEREDITARY ENZYME-SYSTEM PATTERNS

The work of Roger J. Williams is deserving of great attention, because it not only throws light on human alcoholism but also contains much broader connotations. In his work with rats, Williams found that it was relatively easy to render them alcoholics, merely by feeding them deficient diets and placing at their disposal either water or 10 percent alcohol as a beverage. While on marginal diets many of the rats preferred alcohol, but as soon as they were returned to normal diets, containing the essential nutrients, they used the water instead. It would therefore appear that the absence of one or more essential nutrients in the diet produced a craving for alcohol. Translated into clinical terms, this means that the alcoholic may merely be groping for something his tissues crave and which his diet does not contain, or contains in insufficient amounts. For example, the craving for sweets among faithful members of Alcoholics Anonymous is well known. It has been found, in treating human alcoholism, that the use of heavy vitamin supplementation, particularly when vitamin B_{12} is added, has not infrequently changed an alcoholic into a person who "could drink or leave it alone." This method of treatment has been known to succeed where psychotherapy and Alcoholics Anonymous have failed. The theory underlying such results postulates that the individual concerned has a defect in his metabolism as a result of which some essential nutrient is absent or else present in insufficient amounts. Such a defect probably is genotrophic and, at times, hereditary. We must visualize an aggregate of enzyme systems working improperly, but susceptible to favorable change through the addition of certain nutrients, in sufficient amounts, to the habitual diet of the individual concerned. No doubt, as Williams comments, social and psychological factors are not to be dismissed as provocative to alcoholism. It is doubtful, however, if the alcoholic ever is subjected to any specific type of annoyance or frustration different from those experienced by those persons who do not develop alcoholism.

Thus, the craving for alcohol appears to be more somatic than psychic and would seem to rise from some as-yet-undetected type of nutritional deprivation. Since *most* alcoholics partake of an average diet, when they eat, the only valid conclusion is that their physical systems *naturally* require a greater amount of a certain nutrient, or possibly several nutrients, than is normally the case.

The implications of Williams' work are very far-reaching. He believes that everyone possesses a gene-controlled system of enzyme which is highly specific for the individual. The case of alcoholism is merely one example of what may happen when the specific nutrient requirements of an individual are not met. Probably there are innumerable parallels. There may exist a vast number of obscure diseases and disorders which might yield to nutritional therapy when the genotrophic principle is rationally applied.

Good examples of what Williams has in mind may be found among the frustrating blood dyscrasias with which every clinician is familiar. All so-called "nutritional" anemias are by no means simple iron deficiency anemias. At times the "shot-gun" method of treatment, while irrational, proves to be the most effective. We see weak, sickly, anemic women with undiagnosed types of anemia, both of the normocytic and macrocytic type, who fail in succession to respond to iron alone, or to liver extract alone, or to folic acid or vitamin B_{12}, but who at times respond dramatically to large parenteral doses of the complete B-Complex. It would appear also that, in some of these cases, it is essential to give the various remedies *all at one time*, in order to correct the metabolic error which prevents the bone-marrow from doing its normal work.

Thus the nutritional trial-and-error method of attacking unresponsive diseases is one of great importance. By a "mass-action" effect it appears sometimes possible to impart a needed stimulant to some enzyme system, which once mobilized may remain normal for at least relatively long periods.

BOOK REVIEWS

THE BIOCHEMISTRY OF GASTRIC ACID SECRETION. Edward J. Conway, M.D., Sc.D., F.R.S. Charles C. Thomas, Springfield, Ill. 1952. $6.50.

The present volume is concerned with the chemical mechanism involved, or considered to be involved, in the evolution of gastric HCl. The author points out that the secretion of rather strong acid is not a unique biological phenomenon, and occurs in the yeast cell under suitable growth conditions. Conway is the originator of the "redox" theory of gastric acid formation which postulates that a heavy metal catalyst acts as the donor of the hydrogen ion, but he elaborates also on other theories as well. While the book is not easy reading for anyone except a biochemist or physiologist, it is essential for those gastroenterologists who desire to gain a conception of the infinite complexity of acid secretion by the human stomach.

B VITAMINS FOR BLOOD FORMATION. Thomas H. Jukes, Ph.D. Charles C. Thomas, Springfield, Illinois, 1952. $4.00.

Jukes, of the Lederle Laboratories Division of the American Cyanimide Company reviews the megaloblastic anemias and gives special attention to the roles of folic acid and vitamin B_{12} in various anemias. The citrovorum factor is explained. Vitamin B_6 deficiency

and anemia in animals is described. Considerable attention is given to the chemical structure of vitamin B_{12}. Jukes's volume brings up to date the rapidly changing knowledge of hemopoiesis.

SIDE EFFECTS OF DRUGS. L. Meyer, M.D. Elsevier Publishing Company, 300 Park Ave., New York City, 1952, $5.50.

The present volume, written by a doctor from the Netherlands, will, if carefully read, impress the physician with a decided uneasiness with respect to drug therapy in general. All physicians have been impressed in the last ten years by the fact that many synthetic agents which exert excellent and specific effects in a number of diseases carry a certain percentage of unfavorable side-effects, some of which may prove serious and even fatal. For this reason, the average practitioner, in order to play safe, sometimes ignores these newer synthetics completely; yet, on the other hand, other general practitioners seem extremely eager to "try out" everything that is placed on the market and consequently encounter not a few unhappy experiences. Meyer is certainly justified in cautioning against the use of chemotherapeutic and antibiotic agents for the mildest infections not only because of the consequent development of resistant strains of micro-organisms but also because of the considerable percentage of individuals who react unfavorably to these agents. Whether all these unfavorable reactions should be classed as "allergic" is questionable, although possibly most of them are. Meyer does not limit himself to these groups of therapeutic agents, but shows that even the commonest drugs will at times produce fatal results, possibly for reasons poorly understood. We feel that "Side Effects of Drugs" is a timely and valuable book which should be most diligently studied by every medical practitioner.

ANNOTATED BIBLIOGRAPHY OF VITAMIN E (1950 and 1951). National Vitamin Foundation, nc., 150 Broadway, New York 7, N. Y.

The present 100 page volume was compiled by P. L. Harris and W. Kujawski of the Research Laboratories of Distillation Products Industries, Rochester 3, N. Y., a Division of Eastman Kodak Company. Many of the references are accompanied by abstracts of some length, so that the book affords the reader an excellent opportunity to learn the advances in vitamin E chemistry and therapeutics during the past 2 years.

GENERAL ABSTRACTS OF CURRENT LITERATURE

WALTERS, W., GRAY, H. K. AND PRIESTLEY, J. T.: *Advances in the surgical treatment of cancer of the stomach.* Proc. Staff Meet. Mayo Clin., Apr. 9, 1952, 156-161.

In the 3 years 1948-1950, partial gastrectomy was done in 454 cases of gastric cancer with a mortality rate of 6.2 percent and total gastrectomy was done in 62 cases with a mortality rate of 12.9 percent. Surgical removal of gastric cancer is being performed on a larger proportion of patients, and the number of times that total gastrectomy has been done in proportion to partial gastrectomy has increased markedly. The greatest development has been in the technique of total gastrectomy, and this is briefly described. Yet partial gastrectomy should be done in preference when possible.

FRANKLIN, R. H. AND SHIPMAN, J. J.: *Carcinoma of the esophagus.* Brit. Med. J., May 3, 1952, 947-951.

The diagnostic and therapeutic features of 159 cases of esophageal cancer are presented. In diagnosis, frequent repetition of the barium swallow is valuable, especially if a thick barium mixture is used. However, esophagoscopy is more valuable and often reveals tumors which were missed by x-ray. The mortality of the radical operation is approximately 50 percent, but the patient may be returned to a normal state with the ability to swallow restored.

ZUELER, W. W. AND STULBERG, C. S.: *Herpes simplex virus as the cause of fulminating visceral disease and hepatitis in infancy.* Am. J. Dis. Child., 83, 4, April 1952, 321-439.

The virus of herpes simplex can cause a fatal disease in the newborn in the absence of significant cutaneous lesions and can invade the blood stream during herpetic gingivostomatitis in older infants, giving rise to specific herpetic hepatitis. Pathological evidence and clinical data, confirmed in one case by isolation of the virus from the liver, are presented to show the development of a veritable herpes virus septicemia with metastatic lesions in five newborn infants. In these older infants a specific hepatitis was demonstrated.

EVERETT, E. F. AND RIGLER, L. G.: *Cholecystography with telepaque.* Radiology, 58, 4 Apr. 1952, 524-528.

This is another research that indicates that telepaque is an acceptable cholecystographic medium with a somewhat lower incidence of undesirable side-effects. The 3 gram dose is recommended. Visualization of the cystic and common duct often is possible. A possible disadvantage of telepaque is the large number of cases showing opaque material in the colon after ingestion of the tablets, although in this series of cases the opacity did not interfere with satisfactory interpretation of the films. The telepaque tablets are given 10 hours prior to the x-ray film.

DEEB, P. H. AND STILSON, W. L.: *Roentgen manifestations of lymphosarcoma of the stomach.* Radiology, 58, 4, Apr. 1952, 529-535.

Six cases of the title disease are presented. The condition is more frequent than we usually consider it. The presence of a relatively flexible deformity and coarse, irregular rugae suggests lymphosarcoma. Radiation therapy sometimes produces long periods of freedom from symptoms.

AMER. JOUR. DIG. DIS.

Katz, H. L., Sbar, S. and Goldner, M. G.: *The effect of pneumoperitoneum therapy in pulmonary tuberculosis on liver function.* Am. Rev. Tuberculosis, 65, 5, May 1952, 589-595.

Liver function tests were carried out on 25 cases of arrested pulmonary tuberculosis who had been under the influence of pneumoperitoneum from 6 to 21 months, with an average intra-abdominal pressure of plus 12 cm. of water. The study was done to find out if liver function was impaired by this form of treatment and it was found that no impairment of liver function had occurred.

Irwin, D. B.: *Septic jaundice: a complication of peritonitis following gastro-intestinal surgery.* Brit. Med. J., June 28, 1952, 1379-1382.

The author reports 6 cases of jaundice occurring after gastro-intestinal operations complicated by peritonitis. He proposes the name, septic jaundice, for this group. The jaundice began usually with the first week of operation and persisted till death or till the infection subsided. Signs of hepatic parenchymal failure were not observed. Treatment and prognosis are those of the peritonitis. In some of the cases the liver showed a zone of subcapsular necrosis, bounded by a zone of intense congestion of the sinuses, and a layer of pus on the capsule. Peritoneal sepsis is thought to be the cause of the condition.

Tabaka, F. B., Nigro, S. J. and Nora, E.: *Traumatic diaphragmatic hernia complicated by acute traumatic pancreatitis.* Illinois Med. J., 101, 5, May 1952, 269-270.

A man of 25 received severe contusions in the epigastrium and left lower thoracic wall. X-ray revealed a traumatic diaphragmatic hernia containing stomach and colon. At operation it was found to contain also the pancreas which was acutely inflamed and evidencing fat necrosis. In spite of all that could be done he died 13 days after the operation and necropsy showed general peritonitis with fat necrosis of the omentum. Acute traumatic pancreatitis seldom is found co-existing with a traumatic diaphragmatic hernia, but both conditions should be kept in mind in case of physical injury.

Copher, G. H., Wallingford, V. H., Scott, W. G., Zedler, G. G., Hayward, B. and Moore, S.: *Direct irradiation of carcinoma of the liver and biliary tract by the use of radioactive iodine* (I^{131}) *in tetraiodophenolphthalein.* Am. J. Roentgen, Rad. Ther. and Nuclear Med., 67, 6, June 1952, 964-973.

The authors found, both in animal and human experiments, that radioactive tetraiodophenolphthalein is metabolized and excreted in the same manner as the non-radioactive compound. The radiation resulting from the disintegration of the artificially radioactive compound is dissipated primarily within the biliary system and adjacent liver tissue. Computations suggest these radiations are insufficiently strong to be therapeutically effective in cancer of the gallbladder, but may possibly be effective in the liver. It should be possible to treat selectively with radiation by combining radioactive isotopes with elements or compounds that have special affinities for certain organs or body systems. This technique is in effect similar to a "guided missile" and holds promise for treatment of other parts of the body.

Moschcowitz, E.: *The morphology and pathogenesis of cardiac fibrosis of the liver.* Ann. Int. Med., 36, 4, Apr. 1952, 933-955.

Evidence is submitted that the morphological changes of cardiac fibrosis of the liver are the result of portal hypertension of central origin. The author traces these changes, beginning with "nutmeg" liver. Later, centrolobular necrosis occurs. Thereafter, the changes are dependent upon whether a hypertension of the portal circulation is maintained over a sufficiently long period. This occurs usually in constrictive pericardium and often in the terminal stages of tricuspid disease.

Gold, M. A. and Sawyer, J. G.: *Diverticula of the gastrointestinal tract.* Ann. Int. Med., 36, 4, Apr. 1952, 956-978.

This is an exhaustive review of the diverticula of the esophagus, stomach, duodenum, jejunum, ileum, Meckel's diverticulum, and of the colon and deals not only with symptoms and diagnosis but also treatment. True diverticula of the duodenum are very common and symptomless in 98 percent.

Funder, J. F. and Weiden, S.: *The correlation between test meal findings and the histology of the stomach as shown by gastric biopsy.* Med. J. Australia, May 3, 1952, 600-602.

Gastric biopsy and histamine test meal examinations were carried out on 268 patients. The lesions of superficial and atrophic gastritis were found to be associated with a depression of HCl secretion, more severe in the atrophic form. All patients with gastric atrophy (those with P.A. and/or subacute combined degeneration of the spinal cord) have achlorhydria. There is a similar but less profound depression of pepsin secretion in gastritis. Pepsin secretion was demonstrated in some patients with pernicious anemia.

Logan, V. W. and Bobowiec, B. B.: *Gastric ulcer occurring in a patient after lobotomy.* Ann. Int. Med., 36, 4, April 1952, 1093-1097.

A case is presented of a man who was discovered to have chronic non-healing gastric ulcer 10 months after bilateral frontal lobotomy. A review of the literature reveals general agreement that ablation of the frontal cortex will result in increased gastric acidity and motility for an undetermined time after operation.

De, S. N. and Sengupta, K. P.: *The amebic appendix and its perforation.* J. Indian Med. Assn., XXI, 6, March 1952, 243-245.

Invasion of the appendix by *E. Histolytica* is probably much commoner than is usually considered. However, perforation of the appendix due to an amebic ulcer is very rare, and the case presented by the author is the fifth case on record. In regions where amebiasis is common, the possibility of an amebic appendicitis should be considered, since proper medical treatment might prove safer than surgery.

SNEDDON, I. B. AND LEISHMAN, A. W. D.: *Severe and fatal phenobarbitone eruptions.* Brit. Med. J., June 14, 1952, 1276-1278.

The authors described 4 cases of severe allergic reactions to phenobarbitone given in therapeutic doses. The potential dangers of phenobarbitone skin eruptions are probably not sufficiently appreciated. Two of the four cases ended fatally, but post-mortem examination showed no specific pathological changes. One case was saved only by the use of A.C.T.H.

LOCKARD, V. M.: *Lesions of the upper gastro-intestinal tract in infants and children.* Radiology, 58, 5, May 1952, 696-704.

The author describes atresia, stenosis and varices of the esophagus; gastric foreign bodies, gastric ulcer, infantile hypertrophic pyloric stenosis, gastric neoplasms, duodenal obstruction, meconium ileus, intra-abdominal hernia and lymphosarcoma. In one of his cases of gastric ulcer with perforation on the third day of life, autopsy revealed characteristics of chronicity, indicating the ulcer had developed in utero.

MILLER, B. AND NUSHAN, H.: *Phlegmonous gastritis.* Am. J. Roent., Rad. Ther. and Nuclear Med., 67, 5, May 1952, 781-784.

Phlegmonous gastritis may be localized or diffuse and is due to a pyogenic infection of the stomach wall. It is seldom diagnosed clinically. The case described by the authors showed a large fundal filling defect with elevation of the left diaphragm. In spite of intelligent surgical treatment, as well as penicillin therapy, the patient eventually died. The patient was an alcoholic.

WITTS, L. J., BRITTON, C. J. C., DAVIDSON, L. S. P., DAVIS, L. J., SADDOW, A., WHITBY, L., WILKINSON, J. F. AND MOLLISON, P. L.: *The treatment of blood disorders with A.C.T.H. and Cortisone: a preliminary report to the Medical Research Council by the Panel on the hematological applications of A.C.T.H. and cortisone.* Brit. Med. J., 1261-1263, June 1952.

A.C.T.H. and cortisone have been used in 88 patients with diseases of the blood. These preparations appeared to produce remissions in a proportion of cases of acquired hemolytic and thrombocytopenic purpura, but the results were uncertain and unpredictable. The preparations produced complete remission in only 1 out of 36 cases of acute leukemia, and partial improvement in another 8. Effects in all cases were temporary.

HART, F. D., WRAITH, D. G. AND MANSELL, E. J. B.: *Agranulocytosis successfully treated with A.C.T.H.* Brit. Med. J., June 14, 1952, 1273-1275.

A case of agranulocytosis with positive culture of S. hemolyticus from the throat was successfully treated with large doses of penicillin, blood transfusions, the use of streptomycin when the pharyngeal flora changed to staph. aureus, and resort to A.C.T.H. when it was found that the blood counts were not improving. A total of 620 mg. A.C.T.H. was given over a 10 day period. Improvement was noted on the second day. In a month she was perfectly well. It was experimentally proved, on the patient, that her agranulocytosis was due to the use of novalgin (sodium phenyl dimethylpyrazolon methylaminomethane sulphonate: sodium amidopyrine sulphonate). This is the third reported case of drug-induced agranulocytosis responding to A.C.T.H. or cortisone.

DOIG, R. K. AND WOOD, I. J.: *Gastritis: a study of 112 cases diagnosed by gastric biopsy.* Med. J. Australia, May 3, 1952, 593.

A series of 112 cases of diffuse gastritis (48 cases of superficial gastritis and 64 cases of atrophic gastritis) were studied from all angles and compared with a similar series of cases of gastric and duodenal ulcer. Gastric biopsy fragments obtained by the flexible gastric tube were important in diagnosis. The most important etiological factor was chronic alcoholism with malnutrition. Duodenal ulcer patients are usually younger than those with gastritis or gastric ulcer. Probably atrophic gastritis is an outcome of superficial gastritis. The symptoms are similar to those of ulcer, though less severe, and respond to antacids poorly. Atrophy of the tongue, loss of weight and anemia are characteristic of gastritis. There was a pronounced depression of acid and pepsin secretion. Achlorhydria was present in 25 cases of superficial and 52 cases of atrophic gastritis. The chief treatment recommended is a full diet and reassurance.

ANDERSON, D. E.: *Chronic aregenerative anemia of the newborn.* Med. J. Australia, Apr. 26, 1952, 573-576.

Chronic hypoplastic anemia and congenital hypoplastic anemia are other names for the rather rare entity described by the author. The disease is normocytic and normochromic and there is no hepatic or splenic enlargement and no purpuric spots. Apart from the anemia the infant is perfectly normal. Folic acid, liver extract and vitamin B_{12} do no good. Repeated blood transfusions however enable the patient to live for many years, although the ultimate prognosis is not as yet known. The reticulocyte count is low and nucleated red cells are not found in the peripheral blood. The striking feature of the bone marrow is the virtual absence of cells of the erythroblastic series. The disease is a pure red blood cell anemia.

DOIG, R. K. AND WOOD, I. J.: *Gastric and duodenal ulcer: a survey of 141 cases.* Med. J. Australia, May 3, 1952, 602-606.

The authors studied 93 cases of D. U. and 48 cases of gastric ulcer. The average age of onset for D.U. was 36 years, and 44 years for gastric ulcer. A family history of dyspepsia was more common in D.U. than in gastric ulcer. Pain was the most common presenting symptom in both groups, and was usually relieved by food and alkali. 14 patients with D.U. had a previous history of perforation, and nine of these required gastrectomy. While histamine gastric analyses showed high levels of acidity and hypersecretion, there was a tendency for the results to be more nearly normal in gastric ulcer. Rest, sedation, alkalis and atropine were cardinal points in medical treatment. In case surgery was needed the operation of choice was subtotal gastrectomy with gastro-jejunostomy except in older

persons with pyloric block, for whom gastro-jejunostomy was done.

BILLINGTON, B. P.: *Intrahepatic obstructive jaundice.* Med. J. Australia, May 17, 1952, 663-668.

Intrahepatic biliary obstruction is a useful clinical conception to explain certain features during acute hepatitis. The author reports a case of infective hepatitis with a prolonged course which presented features of obstructive jaundice during recovery. Cases of more prolonged obstructive jaundice are mentioned. Two cases are reported of prolonged jaundice suggesting primary biliary cirrhosis, in which autopsy showed intrahepatic carcinoma of the main bile ducts associated with biliary cirrhosis. Thus it is difficult to make the diagnosis of primary hepatic disease in cases of prolonged jaundice with obstructive features, in which no extrahepatic obstruction can be found at laparotomy. It is suggested that the exclusion of an organic intrahepatic bile duct obstruction should be attempted by cholangiography at laparotomy before a diagnosis of biliary cirrhosis is made.

MAHL, G. F.: *Relationship between acute and chronic fear and the gastric acidity and blood sugar levels in Macaca Mulatta monkeys.* Psychosomatic Med., XIV, 3, May-June 1952, 182-219.

Monkeys were studied under conditions both of acute fear and chronic fear. It was found that HCl secretion does not increase during acute fear but does during chronic fear. The stimulation must be such as to produce *sustained* fear. Upon repeated pain-fear stimulation, there was a general reduction in blood sugar, but those hypoglycemic changes did not mediate the increased HCl secretion. The two processes varied independently. This study supports the possibility of anxiety or fear being a possible causative factor in peptic ulcer. Alexander's extension of the emergency theory to chronic emotions and his companion concept of "vegetative retreat" do not adequately fit the experimental findings.

BENZ, E. J., DOCKERTY, M. B. AND DIXON, C. F.: *Polypoid endometrioma of the colon: report of a case in which unusual pathological features were present.* Proc. Staff Meet. Mayo Clin., 27, 10, May 7, 1952, 201-208.

The authors report a case of endometriosis of the sigmoid and rectosigmoid portions of the colon in which the following unusual pathological features were present: formation of a polyp in the sigmoid portion of the colon composed of endometrial tissue, invasion of the overlying mucosa by endometrial glands and stroma and ulceration of the mucosal surface. Of added interest was the presence of an endometrial gland in a regional lymph node. The finding of this lymph node is very unusual and strongly favors the concept of lymphatic embolization in the pathogenesis. At any rate, each focus of endometrial tissue is under the necessity of "menstruating" like a miniature uterus, the products of which tend to open up new clefts for the spread of the endometrial tissue. The menopause and/or castration cause the endometrial tissues to become atrophic. The scar tissue unfortunately remains.

PHILIPP, E. E. AND SKELTON, M.D.: *Congenital diaphragmatic hernia in siblings.* Brit. Med. J., 1283-4, June 14, 1952.

The case is reported of a woman who gave birth to two children each of whom died shortly after delivery, with congenital diaphragmatic hernia. The hernias were both massive, one on the right side, the other on the left, and there is no doubt that the interference with respiration occasioned by the presence of many abdominal organs in the thorax was the cause of death.

ROSENHEIM, M. L. AND KAUNTZ, R.: *Discussion on the medical treatment of hypertension.* Proc. Roy. Soc. Med., 45, 5, May 1952, 269-276.

Low sodium diets, the alkaloids of veratrum, and hexamethonium are chiefly discussed. While low sodium diets are effective, provided less than 200 mg. of sodium daily are imbibed, it is difficult to keep patients on such diets. Half-measures are useless. If the patient is not on a really low sodium intake, he might as well be on a normal diet. Hexamethonium is valuable in the seriously ill patient and, when properly used, excellent effects on left ventricular strain and ocular fundi may be obtained, but it is a potentially dangerous drug, difficult to administer. Veriloid has produced good results in 25 percent of severe hypertensives and fair results in 52 percent. Veriloid will lower the blood pressure in almost all hypertensives except the preterminal malignant and probably the chromaffinoma. By mouth, about 60 percent respond, yet in half of these the effective dose is so close to the toxic dose that hospital treatment is advisable.

TERRY, R.: *Risks of needle biopsy of the liver.* Brit. Med. J., May 24, 1952, 1102-05.

A survey of the literature reveals that over 10,000 needle biopsies of the liver have been performed with modern techniques, with a mortality of 0.12 percent and an incidence of major complications of 0.32 percent. In the author's 207 liver biopsies, there were instances of biliary peritonitis. He makes a plea for a full analysis of cases in future publications so that the risk of specific complications in various disorders may be assessed, especially the risk of biliary peritonitis and hemorrhage in obstructive and parenchymatous jaundice.

WINTHROP-STEARNS PRODUCES DRAMATIC FILM ON X-RAY CONTRAST MEDIUMS

A new motion picture film in color and sound, illustrating the effectivenes of radiopaque compounds in X-ray visualization of the gallbladder and bile ducts, has been produced by Winthrop-Stearns, Inc., for use by the medical profession, it was announced by Dr. Theodore G. Klumpp, president.

The 22-minute film was prepared under the supervision of Dr. Martin Lasersohn, vice-president of Winthrop. It was shown for the first time in December at the annual sales conference of the company's divisional sales managers in New York City. Prints are being made available for showing throughout the country at medical association meetings, hospitals and before other professional groups.

Operative cholangiography and preoperative oral cholecystography are demonstrated in detail in the film, which was made at the Latter Day Saints Hospital, Salt Lake City, Utah. The contrast mediums employed are Diodrast and Telepaque, both supplied by Winthrop. Recently made available, Telepaque has been cited by several investigators as a "superior cholecystographic agent" because its higher iodine content results in better X-ray views of the gallbladder, without toxic reactions in the patient.

Visualization of the common and cystic ducts and much of the biliary tree is also obtained by means of oral administration of Telepaque, the film shows. As a consequence, it is pointed out, Telepaque and Diodrast clearly indicate whether there is a need for instrumental exploration of the common bile duct.

NEW VAPOR COMPOUND SHOWS DRAMATIC RESULTS IN INFANT SUFFOCATION

New York, N. Y.—Suffocation of infants, particularly newborn, resulting from thick mucous secretions can now be prevented in most cases by use of a new drug just made available to the medical profession by Winthrop-Stearns Inc., pharmaceutical manufacturer here.

Called Alevaire, the drug's effectiveness was disclosed by a leading Southern pediatrician following original work with the compound during a study lasting more than a year. The doctor, Dr. Samuel F. Ravenel, Greensboro, N. C., states that Alevaire can be expected to save "a substantial proportion of the 28,000 infants who die annually in the United States from respiratory difficulties." He adds that it has "revolutionized" the treatment of such conditions.

The drug is a chemical combination of a new wetting agent with sodium bicarbonate and glycerine, and is administered as a fine vapor or "fog." The wetting agent belongs to the group of detergent compounds identified as alkylaryl polyether alcohols.

Studies show that Alevaire is effective in treating a wide variety of respiratory diseases complicated by the presence of thick mucous secretions. Some of these diseases are: asthma and bronchopneumonia; capillary bronchitis; poliomyelitis; whooping cough; atelectasis (massive collapse of lung); acute laryngotracheobronchitis, and lobar pneumonia. Treatment with Alevaire, according to one report, has eliminated the need for surgical opening of the windpipe (tracheotomy) in laryngitis and laryngotracheobronchitis in order to admit air into the lungs.

According to Dr. Theodore G. Klumpp, president of Winthrop-Stearns, the chief danger of excessive or thickened pulmonary secretions is "airway obstruction." The result may be collapse of the lung, edema of the respiratory passages, or infection behind the obstruction, possibly requiring surgery or prolonged medical care.

To thin and dissolve the mucous secretions, the Winthrop-Stearns solution is nebulized to a fine vapor. The patient breathes the vapor while in an oxygen tent or similar enclosure. When treating infants and small children, the vapor may be delivered from the nebulizer directly into a croup tent or incubator.

Alevaire is an outgrowth of tests conducted by Dr. Joseph B. Miller and associates, at Sea View Hospital, N. Y. These studies showed that the vapor thinned or dissolved heavy secretions present in pulmonary tuberculosis, thereby suggesting a new approach to the problem of coping with infants' and children's respiratory ailments. When antibiotics or other drugs were indicated in certain conditions, they were used in combination with the vapor.

Most dramatic results with Alevaire were obtained in the treatment of atelectasis in newborn babies, a condition "which does not respond well to any other form of therapy thus far reported," according to Dr. Miller. These infants, suffocating to death, desperately struggle for air which is blocked from entering the lower respiratory tract by the mucous secretions, Dr. Miller explains. Death occurs from fatigue, when the struggle for air depletes muscular strength to the extent that vigorous breathing is no long possible.

Using the vapor, he states, converts a "hopeless" case to an "improving" case within four hours, and to a "normal" one within 24 hours.

Similar impressive conclusions are reported by Dr. Ravenel after a year of clinical testing in which Alevaire "proved an almost infallible weapon" in combatting infant suffocation. Of 15 babies treated for defective lung function, fluid in the lungs, or breathing difficulties of any kind, he notes that all recovered. In sharp contrast, he says, was the 64 per cent mortality rate in 45 babies with collapsed lungs treated by other methods.

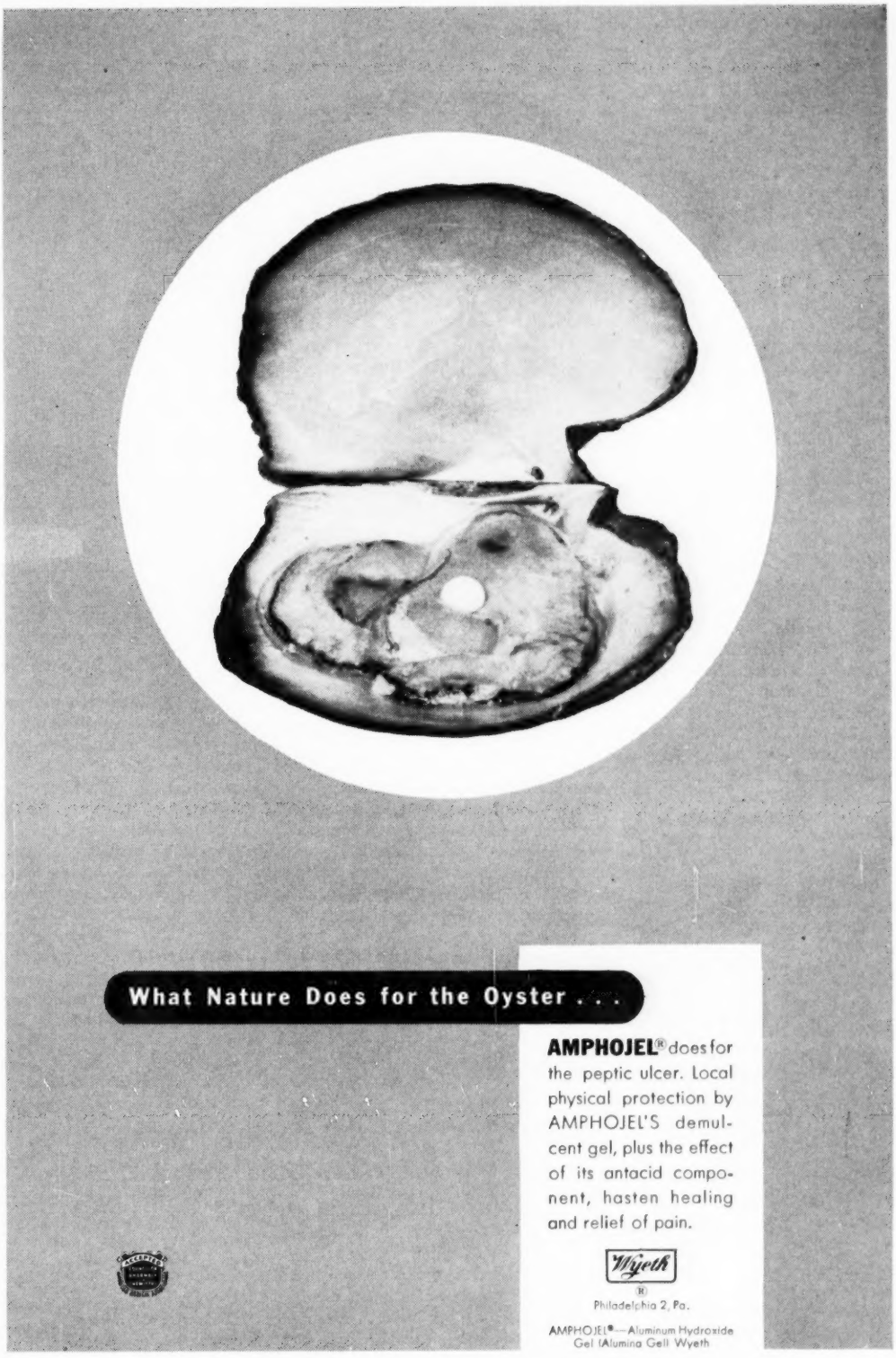
"It enables one to attack these previously discouraging problems with vigor, enthusiasm and confidence," Dr. Ravenel observes.

Alevaire is supplied by Winthrop-Stearns in bottles of 500 cc.

TWO COMPOUNDS COMBINED IN ANTI-EPILEPTIC DRUG

A new drug preparation combining in tablet form two recognized anti-convulsant compounds in order to control epileptic seizures more effectively, has been introduced by Winthrop-Stearns Inc., pharmaceutical manufacturer.

Called Mebaroin, the combination tablet consists of Mebaral, a recognized sedative and anti-epileptic drug, and diphenylhydantoin, also widely used in the treatment of convulsive states. In addition to its anti-epileptic action, Mebaral produces sedation similar to phenobarbital, but is relatively devoid of hypnotic effect. It has been shown to reduce the incidence of epileptic seizures in grand mal and petit mal,



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AMPHOJEL®—Aluminum Hydroxide Gel (Alumina Gel) Wyeth

in most instances without causing drowsiness and lassitude or impairing mental alertness or efficiency.

By combining the therapeutic properties of both compounds, Winthrop points out that it is possible to achieve more effective control of epilepsy and its variants. Being relatively tasteless, Mebaroin is easy to take, the company notes. Winthrop is supplying the product in bottles of 100 and 1,000 scored tablets.

MEXICAN STUDENTS VISIT PARKE, DAVIS & CO.

Forty-one students from the National School of Chemical Sciences at Mexico City visited Parke, Davis & Company, world-wide pharmaceutical firm.

The group included eight men and 33 women. They were on a tour of leading pharmaceutical firms in the United States, traveling by bus chartered in Mexico.

At Parke-Davis, they learned the 86-year old company makes more than 1,000 different products and has been responsible for many historic drug discoveries, ranging from Adrenalin in 1901 to Chloromycetin in 1949. Among other outstanding Parke-Davis developments have been Dilantin for epilepsy, Promin and Promizole for leprosy, Benadryl for hay fever and other allergic conditions, Camoquin for malaria and Kutrol for ulcers.

The visitors inspected Parke-Davis' 51-year-old research building—the first to be erected in America by any commercial institution solely for the purpose of scientific research. The firm's research activities now extend into all important fields of medicine and pharmacy.

P. J. Bosch of the Overseas Division told the students that Parke-Davis has 30 branches and plants in the United States and Canada; nine overseas branches and plants, with others under construction; and numerous distributors elsewhere abroad.

He said the students planned to go from here to Niagara Falls, Toronto and New York City.

A NEW PRODUCT

Donnalate, a new product in tablet form incorporating the pharmacological features of Robalate and Donnatal, is announced by the A. H. Robins Co., Inc., Richmond, Va., for use in the medical management of peptic ulcer. It is described as accomplishing three essentials of therapy, including antacid and buffering action to counteract corrosive acidity, sedation to stabilize emotional tension and anxiety, and spasmolysis to relieve smooth muscle spasticity.

Each Donnalate tablet contains 0.5 Gm. dihydroxy aluminum aminoacetate, 8.1 mg. phenobarbital, 0.052 mg. hyoscyamine sulfate, 0.01 mg. atropine sulfate, and 0.003 mg. hyoscine hydrobromide. One tablet is thus equivalent in active components to one Robalate tablet plus one-half of one Donnatal tablet.

One or two tablets are administered orally at intervals according to the drug dosage-feeding schedule established by the physician, with double doses recommended in the late evening and at bedtime. Robalate or Donnatal may be given supplementally if desired.

Donnalate is supplied as white compressed, engraved, oral tablets in bottles of 100 and 500.

DONNATAL PLUS

Donnatal Plus tablets are announced by the A. H. Robins Co., Inc., Richmond, Va., as a new member of the Donnatal family, combining the sedative-antispasmodic and anticholinergic potency of Donnatal with significant dosage of B complex vitamins frequently deficient in patients requiring spasmolytic therapy.

Each tablet contains the active ingredients of the Donnatal formula, namely hyoscyamine sulfate 0.1037 mg., atropine sulfate, 0.0194 mg., hyoscine hydrobromide 0.0065 mg., and phenobarbital 16.2 mg., plus the B complex factors, thiamine hydrochloride 3 mg., riboflavin 2 mg., nicotinamide 10 mg., calcium pantothenate 2 mg., and pyridoxine 0.5 mg.

Donnatal Plus is described as of especial significance in the treatment of fatigue states associated with abormal carbohydrate metabolism. The belladonna alkaloids protect the pancreatic islet tissue from assault by impulses over the vagus nerve; phenobarbital lessens the psychic factors, and the B complex vitamins stimulate appetite, improving food intake, absorption and utilization.

Three to nine tablets are administered daily according to clinical response. Three tablets provide a full daily therapeutic quota of the important B factors.

Donnatal Plus is supplied in bottles of 100 and 1,000 in green, sugar-coated tablets.

WINTHROP'S ANTI-EPILEPTIC OFFERED IN NEW PACKING

Mebaral, the sedative and anti-epileptic drug produced by Winthrop-Stearns Inc., is now available in a new dosage of three-quarter grain tablets, the company has announced. It will supplement the one-half grain, one and one-half grain and three-grain tablet packings previously supplied. The tablets, scored for division, come in bottles of 100 and 1,000.

Mebaral exerts a strong relaxing and antispasmodic effect, with relatively mild hypnotic action. In addition to reducing the incidence of grand mal and petit mal epileptic seizures, the drug is indicated in treatment of migraine, hyperthyroidism, anxiety states, mild psychoses, arterial hypertension, and other conditions.

FRED M. CULBRETH

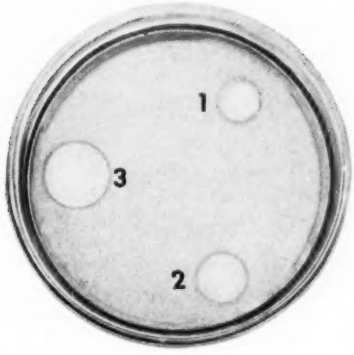
Fred M. Culbreth has been made southern division manager of the A. H. Robins Co., Inc., Richmond, Va., and will establish headquarters at Atlanta, Ga., it is announced by E. Claiborne Robins, company president.

Mr. Culbreth has been a Robins medical service representative since 1946, with a North Carolina territory in the company's Virginia sales division. He received an award as "outstanding salesman of 1951" from the Sales Executive Club, Richmond, Va., branch.

The new southern division manager was born in Raeford, N. C. He attended the University of North Carolina and was in the retail drug business, in Hamlet, N. C., and elsewhere, for a number of years. Mr. Culbreth is married and has three children and is active in civic and church affairs.

LUSYN

Improved Lusyn, indicated in corrective therapy for overstimulation of the parasympathetic and central nervous systems, is announced in a new formula by Maltbie Laboratories, Inc., Newark, N. J. Each tablet now contains 5 mg. in-



Inhibitory action of penicillin (*1*), streptomycin (*2*), and PENSTREP (*3*), on a mixed culture of gram-positive and gram-negative organisms.

For Wide-Spectrum Bactericidal Action

PENSTREP "4:½"	PENSTREP "4:1"

PENSTREP supplies a total of 400,000 units of Crystalline *Penicillin* together with Crystalline *Dihydrostreptomycin Sulfate*—the purest form of dihydrostreptomycin available. PENSTREP provides potent, synergistic bacteri*cidal* action that is effective over a *wide-range* spectrum.

PENSTREP "4:½" contains ½ Gm. of dihydrostreptomycin; PENSTREP "4:1" contains 1 Gm. It is recommended that "4:1" be used for short, intensive periods of therapy, "4:½" for prolonged treatment periods.

Supplied: PENSTREP "4:½": dry mixture for aqueous injection; also, aqueous suspension, ready to inject.

PENSTREP "4:1": dry mixture for aqueous injection.

All product forms available in one- and five-dose vials.

PenStrep*

*PENSTREP is a trade-mark of Merck & Co., Inc.

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for the patient
who needs to
simmer down—

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[ACETYLBROMDIETHYLACETYLCARBAMID SCHENLEY]

Not a Barbiturate
provides ideal **daytime** sedation
without hypnosis

SEDAMYL* quickly relieves the nervous tension and anxiety so often generated by the strains of modern life.[1,2] In 333 patients suffering from nervousness, anxiety, and related psychosomatic complaints, SEDAMYL proved effective for daytime use in 90 percent of cases.[1] Tubes of 20, bottles of 100 or 1000 tablets.

1. Tebrock, H. E.: M. Times 79:760, 1951.
2. Geyer, H. W.: Delaware M. J. 23:255, 1951.

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stead of 2.5 mg. of homatropine methylbromide for more effective dosage, in line with the clinically demonstrated wider safety range of this parasympath*olytic* agent. Phenobarbital content is upped to 15 mg. in place of 8 mg., while the tablet retains 300 mg. of alukalin, or activated kaolin.

Lusyn is used in functional gastrointestinal disorders such as intestinal spasm, biliary spasm, pylorospasm, cardiospasm and irritable colon.

Recommended adult dosage is one or two tablets before meals and if necessary upon retiring. Dosage may be individualized if indicated.

Lusyn is supplied in bottles of 100, 500 and 1,000 scored tablets.

LIPOCHOLAN

Maltbie Laboratories, Inc., Newark 1, N. J., announce Lipocholan, a new product for combined hydrocholeretic and lipotropic therapy. Lipocholan promotes a more pronounced volume of fluid bile and supports functional activity of the liver by prevention or reversal of fatty infiltration within the liver cells.

Presented as a white, uncoated tablet, Lipocholan contains dehydrocholic acid, 125 mg., and choline bitartrate, 350 mg. Though intended primarily for treatment of hepatobiliary disturbances, Lipocholan provides important adjunctive therapy in atherosclerosis, uncontrolled diabetes mellitus, and disturbed fat metabolism.

Lipocholan is supplied in bottles of 100, 500, and 1,000 tablets. The recommended average adult dose is two tablets, two or three times daily, after meals.

TEXAS MEDICAL CENTER

The history of Houston's Texas Medical Center reads like a proverbial "tall Texas tale," and it is tall—but it's also true.

For in the short space of seven years, the Center has become one of the outstanding institutions of its kind anywhere, and it's still growing.

As 1953 begins, the continuous program of development and expansion shows no sign of abating, with new buildings, new facilities for research, and new teaching programs being constantly added to this mammoth health project.

When facilities already under construction and on the drafting boards are completed, the Center will be able to count 3,350 beds, which will represent an outlay of more than $56 million on a 163-acre tract.

During 1951, the Methodist Hospital, a four and one-half million dollar building providing air-conditioned comfort for 315 patients; and the Arabia Temple Crippled Children's Clinic, a one and a quarter million dollar structure, were completed and opened their doors. Thus were important new facilities added for the professional activities that had been going on in the previously completed buildings which include the Veterans Administration Hospital; the original Hermann Hospital, a 250-bed charity and part-pay hospital; the new Hermann Hospital, which has 375 beds and the most modern of equipment; the Baylor University College of Medicine; and the 14-story Hermann Professional Building, which provides the office space for the professional people who carry on the Medical Center work.

Now, work is progressing rapidly on other vital construction projects. The M. D. Anderson Hospital for Cancer Research, which will cost approximately $8 million and have 310 beds, is expected to be the equal of any cancer hospital in the country. It is scheduled for completion early this summer. This hospital, incidentally, is the only project of the Texas Medical Center that has not been financed completely with funds raised by Texas people, being the recipient of a federal cancer fund grant.

The Texas Children's Hospital, which will have 115 beds and be especially equipped to handle difficult cases, is also slated for completion within the next few months at a cost of some $2 million.

Another project now underway that is due to be ready to open its doors early next year is the St. Luke's Episcopal Hospital, a 340 bed institution that will cost $4,700,000.

The University of Texas Dental Branch is also listed among present construction projects, and will represent an outlay of more than $5 million. It will be completed in 1954, as will the one and a quarter million dollar Medical Library of the Houston Academy of Medicine.

But even as buildings are completed and construction on others

begun, the planners of the Medical Center keep looking yet further into the future.

Present plans call for beginning the construction of Jefferson Davis Hospital, a new city-county charity hospital with 700 beds, about midsummer. When it is a reality, the present charity hospital downtown will become the Houston Tuberculosis Hospital.

And the next step forward will be a College of Nursing for the University of Houston, a project being studied at the present time.

But buildings alone do not make a fine medical center, so of special importance are the ways in which the facilities are used and the plans for expansion of the program.

An item of particular interest to Houstonians now is the recent research done in the Baylor University College of Medicine at the Center in the study of polio. The discovery in Houston that flies were carrying polio virus even at a time when there was no polio epidemic has already had effect on the thinking of health authorities and city officials.

Research is also constantly going forward in studying various new drugs and new developments in the treatment of many dread diseases. Cancer, tuberculosis, arthritis, and others get their share of attention, some of the work being done on an independent basis, others in conjunction with national foundations.

A teaching program that follows many channels is an integral part of the Texas Medical Center work, with the Baylor University College of Medicine, the University of Texas Postgraduate School of Medicine, the University of Houston Central College of Nursing, and the University of Texas School of Dentistry sharing the responsibilities of preparing the men and women who will soon take their place in these professions. Through this teaching program, institutions outside the Center have a part in its program, for medical students and interns serve in St. Joseph's Hospital, Southern Pacific Hospital, and the Houston Negro Hospital.

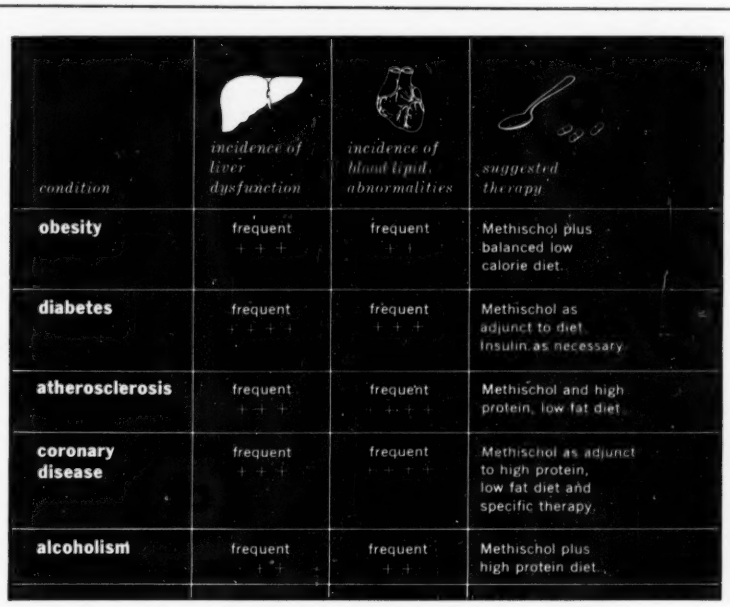
So those who are a part of the Texas Medical Center continue to build, to study, to teach and to treat the sick and suffering; for their self-imposed obligations spur them on.

They have undertaken to become a haven of help for the sick and suffering, a leader in medical education for Texas, and the keystone of advanced medical research in the Southwest.

Borden awards for outstanding research achievements were presented to nine American scientists during 1952, according to an annual directory of award recipients just released by The Borden Company Foundation. The Borden Award consists of a gold medal and $1,000. The awards were instituted in 1936, and since that time presentations have been made to 108 American and Canadian scientists.

The awards are designed to recognize and encourage outstanding research achievements in the United States and Canada, according to the Foundation. They are administered by professional and scientific associations, and are based upon research reported in public documents and scientific journals. Currently there are nine annual awards.

The associations and the nine 1952 award recipients include: The American Dairy Science Association—Emerson W. Bird, Iowa



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the suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls of Methischol provides:

Choline Dihydrogen Citrate*	2.5 Gm.
dl, Methionine	1.0 Gm.
Inositol	0.75 Gm.
Vitamin B_{12}	18 mcg.
Liver Concentrate and Desiccated Liver**	0.78 Gm.

*Present in syrup as 1.15 Gm. Choline Chloride
**Present in syrup as 1.2 Gm. Liver Concentrate

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State College, for fundamental and applied research in dairy manufacturing; The American Academy of Pediatrics—Julius H. Hess, University of Illinois College of Medicine, for his contributions to the care and management of the prematurely born infant; The American Dairy Science Association—John Wm. Hibbs, Ohio Agricultural Experiment Station, Wooster, Ohio, for his researches in calf raising, rumen physiology, milk fever, and the vitamin A and carotene content of milk and roughages.

The American Institute of Nutrition—Max Kleiber, University of California, in recognition of his outstanding recent research on factors involved in the formation and utilization of the constituents of cow's milk; The American Veterinarian Medical Association—Ralph B. Little, III, associate, Rockefeller Institute for Medical Research, for outstanding researches in the etiology and control of dairy cattle diseases; The Poultry Science Association—E. L. Robert Stokstad, Lederle Laboratories Division, American Cyanamid Company, for his work in the isolation and chemistry of folic acid and the production of vitamin B_{12}.

The American Home Economics Association—Clara A. Storvick, Oregon State College, for researches relating to ascorbic acid metabolism, nutritional status, and dental caries; The Association of American Medical Colleges—William S. Tillett, New York University College of Medicine, for research in the mechanism of blood clot liquefaction; and The American Chemical Society, Carrel H. Whitnah, Kansas State College, for his important contributions to knowledge of the physical chemistry of milk, its composition and nutritive quality, and the structure of milk sugars.

Eli Lilly and Company announces the addition to its product list of the following items:

1. Suspension M-120—'Sulfa-Neolin' (Benzethacil with Sulfonamides, Lilly).
2. Ointment No. 75—Neomycin Sulfate, 5 mg. per Gm.
3. Ophthalmic Ointment No. 54—Neomycin Sulfate, 5 mg. per Gm.

Please note that Suspension 'Neolin' (Benzethacil, Lilly), is not available. 'Neolin' is available only in the Suspension 'Sulfa-Neolin' combination.

INDEX TO ADVERTISERS

American Meat Institute VI
Ames Company III
Endo Products, Inc. XIV
Merck & Company, Inc. XI
National Drug Co. ..... IV and V
Organon Inc. VIII
Chas. Pfizer & Co., Inc. .. 3rd Cover
Schenley Laboratories, Inc. XII
G. D. Searle & Co. ..... 4th Cover
The Upjohn Company I
U. S. Vitamin Corp. XIII
Winthrop Stearns, Inc. VII
Wyeth, Inc. ..... 1st Cover
Wyeth, Inc. IX

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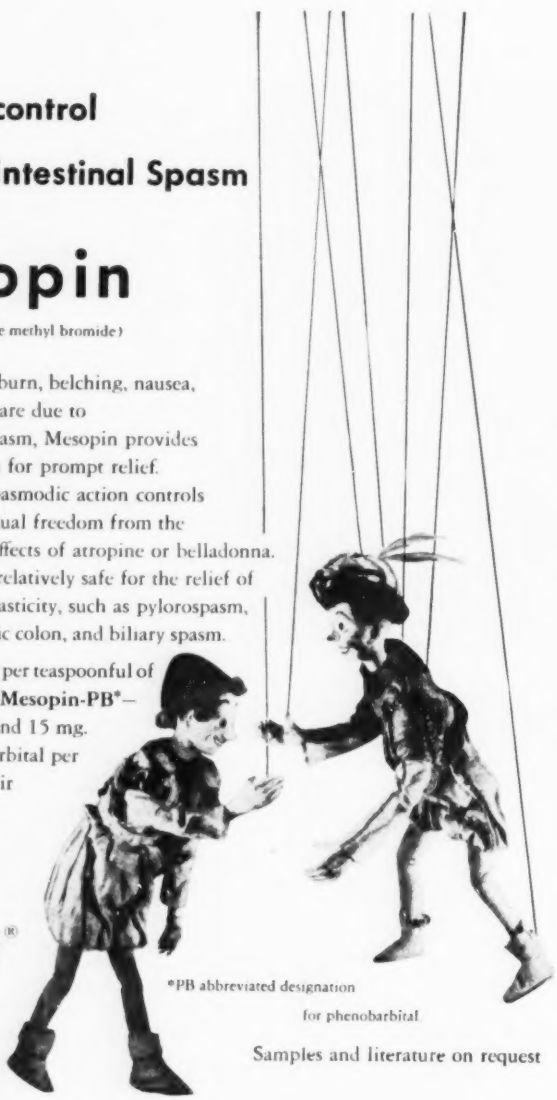
When pain, heartburn, belching, nausea, or unstable colon are due to gastrointestinal spasm, Mesopin provides an effective means for prompt relief. Its selective antispasmodic action controls spasticity with virtual freedom from the undesirable side effects of atropine or belladonna. Thus, Mesopin is relatively safe for the relief of gastrointestinal spasticity, such as pylorospasm, cardiospasm, spastic colon, and biliary spasm.

Mesopin—2.5 mg. per teaspoonful of elixir or per tablet. **Mesopin-PB***—2.5 mg. Mesopin and 15 mg. (1/4 gr.) phenobarbital per teaspoonful of elixir or per tablet.



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*PB abbreviated designation for phenobarbital

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Pure, well-tolerated Terramycin in pleasant raspberry-flavored vehicle.

Each 5 cc. teaspoonful supplies 250 mg. of truly broad-spectrum antibiotic effective against gram-positive and gram-negative bacteria, including the important coli-aerogenes group, rickettsiae, certain large viruses and protozoan organisms.

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appearing
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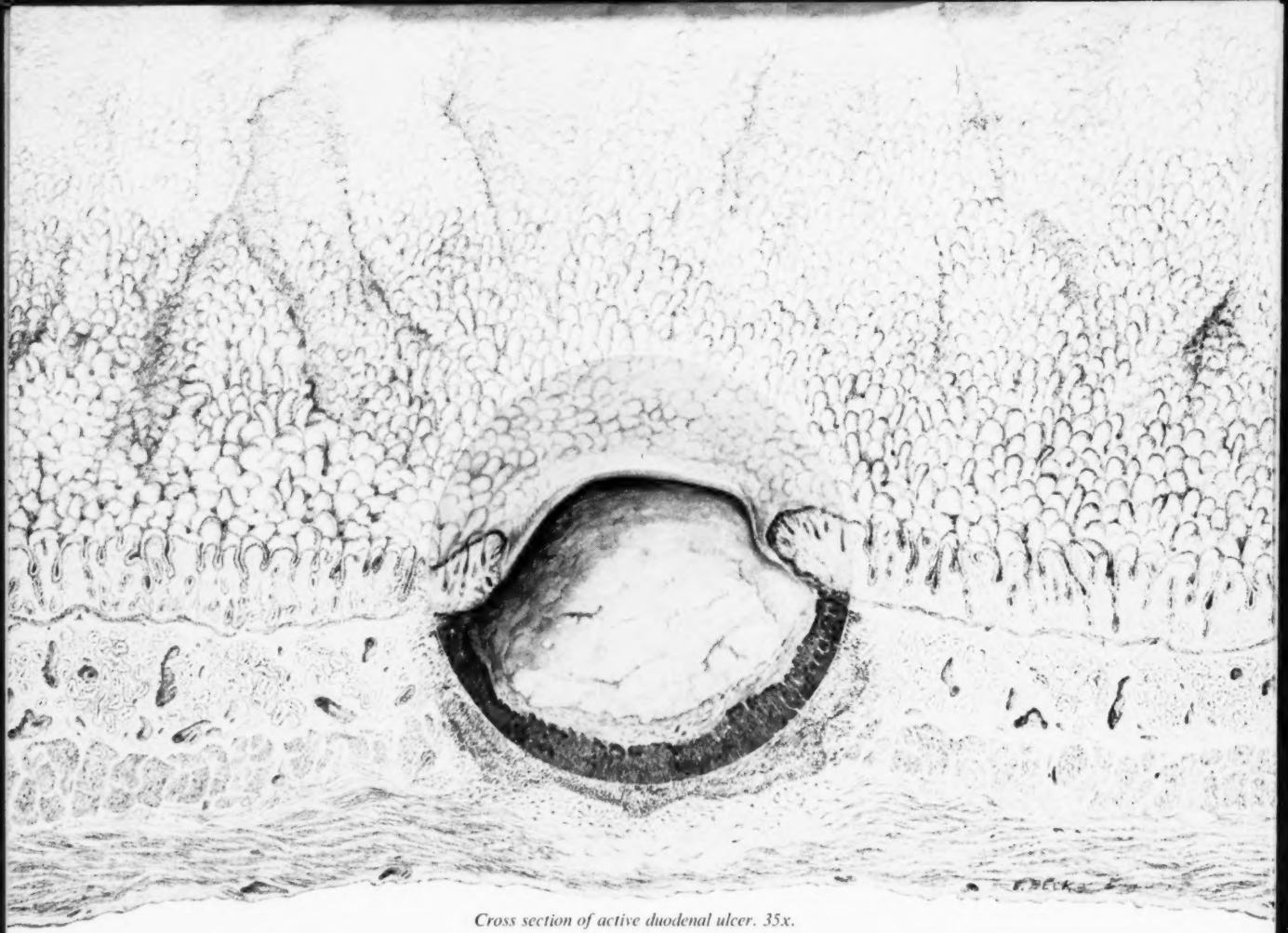

Cross section of active duodenal ulcer. 35x.

Searle Introduces Pro-Banthine*

Smaller dosage, better taste, fewer side effects in new product

The laboratories of G. D. Searle & Co., after continued research in anticholinergic agents, now introduce a new and improved drug for use in the treatment of peptic ulcer, intestinal hypermotility and other parasympathotonic conditions, in its recently perfected Pro-Banthine.

Because of its high potency and greater specificity, Pro-Banthine permits smaller dosage. In a dosage of one tablet (15 mg.) with meals and two tablets at bedtime, minimal side effects may be expected.

Pro-Banthine has a neural inhibiting effect on both the sympathetic and parasympathetic ganglia as well as an atropine-like action on the postganglionic nerve endings of the parasympathetic system.

Provided in oral dosage form—15 mg. sugar-coated tablets.

SEARLE *Research in the Service of Medicine*

*Brand of Propantheline Bromide. Trademark of G. D. Searle & Co.